

This book is inscribed to the memory of
two noble women of the past generation

Rose D. Ficarra

and

Catherine A. Bell

Requiescant In Pace

DISEASES *of the* THYROID *and* PARATHYROID GLANDS



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Formerly Associate Visiting Surgeon (Head and Neck Surgery) Brooklyn Cancer Institute Brooklyn N.Y.
Consultant in Thyroid Surgery Yonkers Professional Hospital Yonkers N.Y.



Intercontinental Medical Book Corporation

~~~~~New York 1958~~~~~





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**Dedicated to
the American Men of Medicine, Surgery and Research
Who Pioneered and Assisted in
the Flucidation Management and Treatment of
Thyroid Diseases**

Contents

| | |
|--|------|
| <i>Foreword</i> | ix |
| <i>Preface</i> | xii |
| <i>Introduction</i> | xiii |
| 1 CHRONOLOGIC RESUME OF THYROID AND PARATHYROID HISTORY | 1 |
| 2 ANATOMY AND PHYSIOLOGY OF THE THYROID GLAND | 9 |
| Brief Anatomic Review of the Thyroid Gland | |
| Physiology of the Thyroid Gland | |
| Biochemistry of the Thyroid Gland | |
| hydrolysis of thyroglobulin | |
| circulating thyroid hormone | |
| Summary of Recent Knowledge of Biochemistry of the Thyroid Gland | |
| 3 THE CLINICAL PICTURE OF HYPERTHYROIDISM | 19 |
| Signs and Symptoms of Hyperthyroidism | |
| exophthalmic goiter | |
| Etiology of Hyperthyroidism | |
| thyroid changes in goiter | |
| colloidophagy | |
| thyroid disturbances in terms of the matrical theory | |
| Methods for Determining Thyroid Function | |
| a new and simple test for hyperthyroidism | |
| Recognition of Neck Masses | |
| Endemic Goiter | |
| calcium as a goitrogenic agent | |
| Aureomycin and the Thyroid Gland | |
| Case Report Hyperthyroidism in an American Indian | |
| Addenda | |
| 4 HEMORRHAGE AND PAIN IN THE THYROID GLAND | 51 |
| Thyroid Enlargement Due to Hemorrhage | |
| Pain as a Symptom in Thyroid Disease | |
| Toxic Adenoma (Plummer's Disease) | |
| Apathetic Hyperthyroidism | |
| 5 MENTAL SYMPTOMS IN HYPERTHYROIDISM | 57 |
| Psychosomatic Symptoms and Borderline Hyperthyroidism | |
| Phobia as a Symptom in Hyperthyroidism | |
| Hyperthyroidism and Neurosis | |
| Addenda | |

| | | |
|----|--|-----|
| 6 | THIOCYANATE MYXEDEMA FOLLOWING THYROIDECTOMY | 66 |
| | Mental Symptoms in Myxedema | |
| | Ascites in Myxedema | |
| | Endemic and Sporadic Cretinism | |
| | skin test for myxedema in children | |
| 7 | HYPERTHYROIDISM PUBERTY AND THE REPRODUCTIVE PROCESS | 71 |
| | Physiological Enlargement of the Thyroid | |
| | Diagnosis and Differential Diagnosis | |
| | Treatment | |
| | Pregnancy | |
| | Effect of Thyroid Therapy on Menstruation and Sterility | |
| | The Thyroid and Reproductive Function | |
| 8 | THYROID DISEASE AND THE CLIMACTERICUM | 89 |
| | Menopause and Hyperthyroidism | |
| | Thyroid Surgery in the Elderly | |
| 9 | THYROIDITIS | 91 |
| | Struma Lymphomatosa | |
| | etiology and pathology | |
| | clinical picture | |
| | diagnosis | |
| | treatment | |
| | prognosis | |
| | Résumé on Hashimoto's Disease | |
| | De Quervain's Disease | |
| | The Reticuloes | |
| | Treatment of Non suppurative Thyroiditis | |
| | Hurthle Cell Adenoma of the Thyroid | |
| 10 | THYROID CRISIS | 109 |
| | Theories of Thyroid Crisis | |
| | The Hepatothyroid Relationship | |
| | laboratory tests on the liver in thyroid disease | |
| | Clinicopathological Evidence for the Hepatothyroid Concept | |
| | Anoxia and Hepatic Disease | |
| | Comments and Conclusions on Thyroid Crisis | |
| | Addenda | |
| | Hyperthyroidism and Myasthenia Gravis | |
| 11 | MANAGEMENT OF HYPERTHYROIDISM | 130 |
| | Radioactive Iodine | |
| | effects of radioactive iodine | |
| | case history of patient treated with radioactive iodine | |
| | Treatment of Thyrotoxicosis with Potassium Perchlorate | |
| | The Antithyroid Drugs | |
| | effects of the antibiotics on the thyroid gland | |

| | | |
|----|--|-----|
| | Surgical Treatment | |
| | practical aspects of thyroidectomy | |
| | Treatment of Post thyroidectomy Tetany | |
| 12 | COMPLICATIONS DURING AND AFTER THYROIDECTOMY | 167 |
| | Immediate Postoperative Care | |
| | Transient Cardiac Arrhythmia following Thyroidectomy | |
| | Elective Tracheotomy following Thyroidectomy | |
| | Substernal and Intrathoracic Goiter | |
| | Phantom Goiter | |
| | Tracheotomy and Thyroidectomy | |
| | complications of tracheotomy | |
| 13 | THYROID CANCER | 183 |
| | Nodular Goiter and Carcinoma | |
| | Treatment of Thyroid Cancer | |
| | palliative resection | |
| | radiation therapy | |
| | Thy tropin following thyroidectomy | |
| | Addenda | |
| | Persistent and Recurrent Thyroid Diseases | |
| 14 | ECTOPIC THYROID AND OTHER ANOMALIES | 211 |
| | Carcinoma in Chronic Thyroglossal Anomalies | |
| 15 | EXOPHTHALMOS | 223 |
| | Exophthalmos in Thyrotoxicosis | |
| | Otolaryngologic Causes of Exophthalmos | |
| | Progressive Postoperative Exophthalmos | |
| | Treatment of Exophthalmos | |
| 16 | HYPERTHYROIDISM | 234 |
| | Laboratory and Clinical Picture | |
| | Relationships Between Parathyroids and Bone Diseases | |
| | Secondary Hyperparathyroidism | |
| | Familial Hyperparathyroidism | |
| | diagnosis | |
| | treatment | |
| | Effects of Parathyroidectomy and Tetany on Liver Cell Permeability | |
| | Carcinoma of the Parathyroid Gland | |
| | <i>Bibliography</i> | 255 |
| | <i>Index</i> | 287 |

Foreword

SINCE KOCHER first focused the attention of the medical profession on the importance of treating goiter and other diseases of the thyroid gland surgically, there has developed an ever increasing desire for knowledge concerning this subject.

The unfortunate sequelæ of postoperative myxedema resulting from the first series of thyroidectomies by the father of thyroid surgery only stimulated the efforts to reduce the complications and improve the end results. The discoveries of Cull and Kendall and of others added greatly to our knowledge of the functions of the gland, but the surgical treatment of hyperthyroidism with its attendant dangers and mortality proved an ever increasing challenge. The late Dr. George Crile sought to reduce the hazards by the use of anæsthesia, a suture, by packing the incision with flanne gauze and performing a secondary closure or by the use of sympathectomy of the adrenal glands. It was Dr. Miles Porter who injected boiling water into the substance of the gland to cause necrosis and destruction and thereby to lower its toxicity. Others sought to accomplish more by the drastic use of weak solutions of carbolic acid and other solutions.

Dr. Charles Mayo and his associates depended largely on the careful selection of cases of toxic goiter for surgery, the proper timing of surgery and in particular on the use of ligation and stage operations. Despite the precautions patients continued to die. Many died without the benefit of any surgery, others following a stage operation and others who appeared to be good surgical risks following a thyroidectomy. It was difficult and often impossible to predict which patient would develop a postoperative crisis. There was no successful means of combatting or treating even the cases of postoperative crisis. Intravenous feeding was yet to be discovered, blood transfusions were only a little understood, packing the patient in ice to lower his fever and quiet the delirium saved some, the subcutaneous use of fluids helped others. There was disagreement as to whether digitalis was helpful or harmful in combatting cardiac complications. Some felt that the use of deep x-ray therapy, as advocated by Pfahler and others, was preferable to surgery. After years of study it became evident that this agent merely retarded the disease and that the lowered degree of hyperthyroidism continued to cause a serious and lasting damage to the cardiovascular system.

Out of this maze of conflicting ideas and therapy suddenly came one of the truly great discoveries in the medical age. When in 1922 Plummer suggested the use of Lugol's solution of iodine in the preoperative prepara-

tion of cases of hyperthyroidism the surgical treatment of this condition was revolutionized. Cases that formerly could never have gone to surgery were now so successfully prepared that thyroidectomy could be performed with little danger of the dreaded crisis occurring. Further study, however, was needed. Crises still occasionally occurred and it soon became apparent that iodine was just as important in the postoperative as in the preoperative care.

Then another sequela developed. Because iodine was given to all types of goiters, hyperthyroidism developed in certain nontoxic nodular goiters receiving the drug, while cases of Graves' disease long continued on therapy became iodine fast or resistant and when operated upon went into a crisis and died just as if they had never been treated.

Finally it was shown that iodine had little or no benefit in patients having toxic nodular goiters. As a consequence the risk of surgery in these cases was often great and no manner of preoperative therapy seemed to prevent the serious and occasionally fatal reactions.

The improved surgical teamwork developed at the large goiter clinic, namely the Mayo, Crile, and Bailey Clinics in this country, reduced surgical complications and lowered the mortality until it was less than 1 per cent in the cases of Graves' disease.

In 1941 Dr. Astwood and his associates found the answer to the successful treatment of toxic nodular goiter. Their discovery of thiouracil and subsequently of propylthiouracil, tapazole and other preparations enables these cases to be treated so successfully that thyroidectomy could be performed with no greater risk than in the nontoxic cases. In Graves' disease these agents appear to have no particular advantage to iodine fast cases.

Finally there came to the armamentarium of the thyroidologist radioactive iodine and at first it seemed that this agent might largely displace surgery in the treatment of goiter. Soon it became evident that it had no place in the nontoxic nodular goiter; it has no special advantage over the antithyroid drugs in the toxic nodular goiter; it is helpful but not curative in malignant goiter. It has been successfully used, however, in a large series of cases of Graves' disease. Whether in time I^{131} will displace surgery in the treatment of this disease only time will tell. At most of the large thyroid clinics in this country, thyroidectomy is still the method of choice after studying I^{131} for nearly ten years. Its use has proven helpful as a diagnostic aid, but it should be observed that hyperthyroidism is a progressive disease and if the diagnosis is not immediately apparent, the clinical signs and symptoms will soon become evident.

The author of this book has had the opportunity of studying this subject in a large medical center for many years and is well versed in all its

various phases. More especially, he had the opportunity of studying under one of the finest of all American surgeons and a great student of thyroid, the late eminent Dr. Frank E. Bailey.

Although progress in the development of our knowledge of this field has been slow, its course has from time to time been interrupted by brilliant contributions such as those cited, and it is important that texts such as this keep the profession advised of the current status of the subject. From a survey of the objectives and aims of the author and of the titles from the contents, I am sure that this book will prove a helpful and valuable guide to all those who are interested in the field of thyroid surgery.

ARNOLD S. JACKSON, M.D.

Madison, Wisconsin

Preface

THE RECENT discoveries in medical science have materially changed the diagnosis and treatment of many diseases. This revolutionary evolution in the management of diseases is clearly illustrated in our modern treatment of thyroid disease as compared with methods used only a few years ago. The era of the antithyroid compounds and radioactive iodine is of very recent origin. The bringing together between the covers of one book of the most modern therapeutic methods in thyroid disease fulfills a very real need for the medical student, intern, resident, general practitioner, internist, and general surgeon who encounters an occasional case of this malady. The thyroid specialist still sees quite frequently patients who are in serious difficulty because complications, such as leukopenia, agranulocytosis, and the innocent thyroid nodule which has metastasized, were not recognized at their onset. This text will be an invaluable aid to all who treat diseases of the thyroid. It will enable the reader to have readily available an authoritative source book on Diseases of the Thyroid and Parathyroid Glands.

Dr. Ficarra's book is no mere compilation from previous texts. It finds its origin in his wide experience in the diagnosis and treatment of thyroid disease. From this experience he has chosen wisely and emphasized well the most necessary facts on this subject. There is no greater field for good management than in that presented by diseases of the thyroid gland. Dr. Ficarra has done the profession a real service in emphasizing the importance of competent care for this group of patients.

I heartily recommend this book to all persons associated with medicine and surgery. All can benefit from the scientific and practical knowledge contained in the pages of this book. Anyone interested in the thyroid or parathyroid glands should have a copy of this book in his library. Every one from the medical student to the thyroid specialist will not have completed his medical education until he has read this most excellent presentation on thyroid and parathyroid disorders.

WILLIAM TREVOR, M.D.
New York City, N.Y.

Introduction

THIS VOLUME on *Diseases of the Thyroid and Parathyroid Glands* has been published not because it is believed to contain any new revelations for the master thyroid surgeon but because it contains factual knowledge on thyroid diseases which should be made known to the general surgeon interested in thyroid surgery. This book therefore is the literary product of a general surgeon who is interested in managing and operating upon patients with surgical disorders of the thyroid gland. It is an accumulation of knowledge gained by an average general surgeon with an average surgical practice in an average American community.

Many of the questionable phrases in the management and treatment of thyroid diseases may not be acceptable to all those who may chance to read this book. For example, the technique described here should not be construed as the only procedure or the preferential routine of thyroidectomy. It is the method to which I was initiated during my formal period of surgical training and therefore has become the technique to which I am accustomed. Any technique of thyroidectomy which the surgeon finds satisfactory should be acknowledged as the method of choice for him.

As in many other surgical matters an *open mind* and a right to express an opinion is an inherent attribute of the American surgeon. This characteristic is reflected in the pages of this book, namely, that in many instances the written words are an expression of the author's opinions, personal observations, experiences and studies on thyroid diseases. It is hoped that the observations and studies will be interesting and informative to those of my colleagues who may read this text.

In the not too distant past a more distinct differentiation existed between the medical and surgical diseases of the thyroid gland. At that time hypothyroidism was the chief medical disease. Hyperthyroidism and neoplasms in their myriad forms were considered to be surgical diseases of the thyroid gland. However, since 1941 as a result of certain new discoveries medical management has invaded the realm of surgical treatment for thyroid diseases. Specific reference is made to the advent of the antithyroid drugs and radioactive iodine.

Both the thiourea drugs and the isotopes have been used to treat hyperthyroid patients. The success of these nonsurgical methods has been satisfactory so that it is proper to assume that more hyperthyroid patients are the recipients of the therapeutic agents than the surgeon realizes. It is doubtful, however, that these methods will completely eliminate the

services of the thyroid surgeon. In this treatise therefore, consideration must of necessity be given to the medical regimen employed in the management of thyroid diseases. Both of these medical methods will be discussed subsequently in their proper location.

In addition emphasis will be placed upon some of the unusual aspects of thyroid disease. Many of these are infrequently discussed in many thyroid presentations or have not been mentioned at all. This present discussion will likewise emphasize certain other aspects of thyroid disorders which should be common knowledge to all those concerned with the treatment of thyroid patients.

BERNARD I. FICARRA, M.D.

I

Chronologic Résumé of Thyroid and Parathyroid History

| | |
|-------------|--|
| 1600 B C | Ancient Chinese used burnt seaweed and sponges in wine to treat goiter |
| 1400 B C | In the Ayurveda of Suhruta (India) goiter is called galagandha. It is attributed to derangement of the neck tendon |
| 460-350 B C | Hippocrates considered goiter to be a deformity attributed to drinking of snow water |
| 23-79 A D | Pliny the Elder Roman maintained that goiter is caused by impurities in the water |
| 25-50 | Celsus refers to the dangerous operations for the removal of a goiter in his De Struma (Opera Lib VIII) |
| 130-200 | Calen wrote of the two neck gland in which moisture is generated. These are of puggy nature and from them the humor oozes out and trickles down there being no necessity for ducts. Thus he described the hormonal function of the thyroid gland. Calen thought that the thyroid secretion lubricated the larynx |
| 560 | Aetius regarded exophthalmic goiter as a variety of aneurysm |
| 629-690 | In the Books of Paul (Paulus Aeginetus) reference is made to the fact that in those days physicians utilized the term bronchiocoele for goiter |
| 944 | In the Royal Book of Holy Abbas (Persian) we are informed that "For goiter in which medication is of no avail surgery is necessary" |
| 1013-1106 | Albucasis mentions an operation for goiter which disease he calls elephantiasis of the throat |
| 1136 | In the Persian system of medicine (Jurjani) attention is called to the concurrence of exophthalmos and goiter |
| 1170 | Roger of Salerno alluded to goiter and cretula and recommended their treatment with sponge ashes |

- 1235-1311 Arnold of Villanova suggested burnt sponge and seaweed to treat thyroid diseases
- 1271 The earliest reference made by an Occidental writer to goiter in China is recorded by Marco Polo in his travelogue. He wrote 'They are in general afflicted with tumors on the throat occasioned by the nature of the water which they drink.'
- 1418 Valescus de Taranta popularized the treatment of goiter as advocated by Arnold of Villanova in the previous century.
- 1452-1519 Leonardo Da Vinci stated that the thyroid glands (he thought there were 2) were made to close the gaps where the neck muscles were absent, and that the thyroid separated the trachea from the clavicle.
- 1520-1575 Eustachius termed the thyroid glandula laryngea, and applied the name isthmus to the part connecting the two lobes.
- 1543 The great anatomist Vesalius described the thyroid as 2 glands, one on each side of the root of the larynx, which secrete a humor.
- 1563 Realdo Columbus pointed out for the first time that the thyroid gland normally was relatively larger in women than in men.
- 1601 Giulio Casserio described the thyroid as a single organ consisting of 2 parts. He concluded that this gland had no secretory effects.
- 1602 Felix Plater referred to cretins in connection with mental deficiency.
- 1619 Fabricius d' Aquapendente was the first to localize the thyroid gland as the anatomical seat of goiter.
- 1657 Hoefler discussed the causation of goiter by air, water and food.
- 1657 The term bronchocele was used by Paul Aeginetus (from the Greek meaning windpipe) as a synonym for goiter. It is recorded in English for the first time in 'A Physical Dictionary.'
- 1659 Thomas Wharton did not clearly distinguish the thyroid from the submaxillary glands but he called it thyreoidea, from the Greek meaning 'an oblong shield.' He

- believed the thyroid gland dried up the superfluous moisture from the recurrent nerve
- 1663 Malpighi was the first to investigate the internal structure of the thyroid gland
- 1698 William Cowper concluded that the thyroid had the same 'office' as the thymus
- 1711 Verecellani of Asti stated that the thyroid was a receptacle for worms
- 1717 Heister refutes the postulate of Verecellani
- 1720 Blouette first called attention to the minute structure of the thyroid gland by stating that the vessels seem to communicate with each other
- 1770 Haller classified the thyroid as a ductless gland pouring a specific fluid into the veins and so into the general blood circulation
- 1779 The word Hypothyroidism appears in the Oxford Dictionary
- 1786 De Saussure ascribed cretinism to the concentrated air in deep valleys rather than to water
- 1786 Parry described the first recorded case of the symptoms corresponding to the syndrome of hyperthyroidism
- 1789 Vincenzo Malacarne published the first important book on endemic goiter
- 1792 Pierre Deault isolated and ligated the superior and inferior thyroid arteries before cutting them and was apparently the first to dissect the firmly adherent gland from the trachea
- 1800 Antonio Testa reports the prominence of the eyes and the cardiac symptoms in hyperthyroidism
- 1802 Flajani reports the case history of a young Spaniard with severe hyperthyroidism listing the symptoms accurately without realizing the true significance of the three main symptoms
- 1811 Bernard Courtois discovers iodine
- 1813 Sir William Blizard performs the first thyroid artery ligation on man
- 1815 Sir Humphrey Davy discovers iodine in marine products
- 1820 Coindet of Geneva suggests that the beneficial effects in

treating goiter with marine products might be due to the iodine

- 1824 Angellini found iodine in certain natural springs which were known to cure goiter
- 1827 Sir Astley Cooper described his experimental thyroid ectomies the first to be performed in England
- 1829 Magendie presents to the Royal Academy of Sciences 'the motives which have induced M. Lugol to employ an aqueous solution of iodine'
- 1830 Robert Graves first presented a full picture of exophthalmic goiter recognizing the rapid heart, protruding eyes and nervousness as well as the enlarged thyroid
- 1836 P. J. Roux reports in the Paris Archives of Medicine a case in which a goiter was removed surgically. The operation was performed on March 26, 1837
- 1840 Carl Von Basedow of Merseburg described the classic symptoms of hyperthyroidism which gave rise to the 'Merseburg triad'. The triad is thyroid enlargement, exophthalmos and tachycardia
- 1846 Robert Liston gave his opinion to be that tumors of the thyroid should be treated surgically
- 1848 Diffenbach states the operation for goiter is one of the most thankless most perilous undertakings which if not prohibited should be restricted
- 1849 Prevost suggests that goiter was due to iodine deficiency in drinking water. He suggested that the iodine in certain salts protected against goiter
- 1850 Luigi Porta ligates the thyroid arteries to produce ischaemic atrophy of the gland
- 1851 Victor Von Bruns successfully removes several thyroid nodules
- 1854 William Stokes describes hyperthyroid heart disease
- 1855 Kaeft proposed the use of iodized salt to prevent goiter
- 1859 Moritz Schiff concludes that the thyroid gland had an internal secretion
- 1859-1876 Chatin establishes that goiter and cretinism are due to the absence of iodine in the drinking water and in the air
- 1860 Richet gave the French Academy of Medicine his classical description of iodine toxicity

- 1863 Charcot describes tumor of the hand as a sign of exophthalmic goiter
- 1864 Friedrich Wilhelm Albrecht von Graefe describes the failure of the upper lid to move downward promptly and evenly with the downward movement of the eyeball of ten men in hyperthyroidism with exophthalmos
- 1870 An advance in the use of hemostatic forceps occurs at the *Schiebervorrichtung* of Fricke. The efficient control of hemorrhage by means of the hemostat replaced the crude cautery, the artery hook, the ligature carrier, the mass ligature and the crushing forceps
- 1871 Austin Flint states from the point of view of physiology the thyroid gland may be removed without interfering with any of the vital functions
- 1879 Halsted popularizes the use of the hemostatic forceps in America
- 1880 Parathyroid glands discovered by Sandstrom
- 1883 Koerber and Reverdin describe the effects of total excision of goiter in 100 patients
- 1883 Sir Felix Semon puts forward the view that cretinism, myxedema and postoperative myxedema were all due to thyroid insufficiency
- 1883 Babnow begins a chemical investigation of the thyroid
- 1884 Boeckel is the first to use the thyroidectomy transverse collar incision in the normal lines of skin cleavage
- 1886 Sir Victor Horsley in *Lancet* advances the theory of the thyrogenous origin of exophthalmic goiter, asserting that the thyroid body is first affected and that all the symptoms are explainable by an altered function or dysthyroidism
- 1889 Biondi (with Hadenham) establishes histologically that both the thyroid and parathyroid glands are secreting glandular organs
- 1890 American surgeons commence to operate for thyroid disease. The leaders in this field are W. S. Halsted, C. H. Mayo and G. W. Crile
- 1891 Brown-Séquard with D'Arsonval describes 'chemical messengers' which in later years are called hormones
- 1891 Murray uses an extract of the thyroid gland to treat a patient with hypothyroidism

- 1891 Von Recklinghausen describes the autopsy bone findings in osteitis fibrosa cystica
- 1892 Mackenzie and Fox independently record their successes in the administration of thyroid preparations
- 1892 Gley describes the importance of the parathyroid glands
- 1893 Kocher postulates that iodine most probably occurs in the thyroid and is its most fundamental constituent
- 1895 E Brummann confirms the presence of iodine in the thyroid gland
- 1895 At first regarded as accessory thyroids, the parathyroids are stated by Kohn to be anatomically and physiologically distinct from the thyroid
- 1895 Magnus Levy introduces the experimental method of determining thyroid disturbances which later leads to B M R studies
- 1895 George W Crile Sr introduces his theory of anoci- as ociation for the reduction of surgical shock. This lessened the surgical mortality of toxic thyroid patients and instituted the era of "testing" the thyroid under narcosis
- 1896 Hutchinson discovers that iodine of the thyroid gland is bound to a globulin
- 1896 Riedel of Jena describes ligneous thyroiditis
- 1896 Vas ale and Generali show that the parathyroids have a function distinct from the thyroid
- 1898 Kocher establishes a definite procedure for thyroidectomy and popularizes the incision of Boeckel which in later years is called the Kocher incision
- 1899 Oswald attempts to chemically isolate the thyroid principle
- 1900 Vas ale and Generali elucidate the function of the parathyroid glands and described postoperative tetany
- 1907 Erdheim, the pathologist, describes parathyroid tumors with skeletal decalcification
- 1908 MacCallum shows that tetany in parathyroidectomized dogs is due to a lowered blood calcium
- 1909 Emil Kocher receives the Nobel Prize for medicine. At this time he had operated upon more than 9 000 patients. His mortality was less than one half of 1%

- 1909 Dunhill of London points out that thyroid heart disease can be cured by thyroidectomy
- 1912 Hashimoto describes struma lymphomatosa
- 1913 Charles De Syon advances the hypothesis that hyperthyroidism was due to "An excessive mental stress, fear, rage or grief—which causes an excessive catabolism etc. Thus he calls attention to the psychic component of hyperthyroidism
- 1915 David Marine and associates find that living thyroid tissue has an affinity for iodine and that it is rapidly stored in the gland no matter how the iodine is given
- 1915 Binger and Fitz attempt to produce exophthalmic goiter experimentally (Am J Physiol)
- 1917 Kendall of Mayo Clinic call the chemical substance in thyroid "Thyroxine" and isolates it from the thyroid
- 1919 Imm Coetich becomes Professor of Surgery at Long Island College of Medicine and establishes the first thyroid clinic in Brooklyn New York
- 1923 Plummer and Boothby publish their investigations on the use of iodine in hyperthyroidism. This gave a great stimulus to the surgical treatment of hyperthyroidism
- 1924 Hanon isolates the parathyroid hormone
- 1925 Felix Mandl of Vienna proves the true nature of parathyroid adenoma
- 1926 Collip prepares a parathyroid extract that can raise blood calcium
- 1926-1930 Harrington of London isolates and crystallizes thyroxine. He proves that the molecule contains 4 iodine atoms attached to 2 aromatic rings
- 1926 Abelson observes that the toxic effects due to feeding thyroid gland to rats could be lessened by diets rich in cod liver oil or egg yolk
- 1927 Lahey Clinic is founded in Boston by the late Dr F H Lahey whose staff has made noteworthy contributions to the management and surgical treatment of thyroid diseases
- 1936 De Quervain describes a form of thyroiditis which now bears his name
- 1943 Astwood and others introduce the thiouracil drugs in the treatment of hyperthyroidism

- 1891 Von Recklinghausen describes the autopsy bone findings in osteitis fibrosa cystica
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- 1895 George W. Crile, Sr. introduces his theory of "anoci association" for the reduction of surgical shock. This lessened the surgical mortality of toxic thyroid patients and instituted the era of "stealing the thyroid under narcosis"
- 1896 Hutchinson discovers that iodine of the thyroid gland is bound to a globulin
- 1896 Riedel of Jena describes lignous thyroiditis
- 1896 Vassale and Generali show that the parathyroids have a function distinct from the thyroid
- 1898 Kocher establishes a definite procedure for thyroidectomy and popularizes the incision of Boeckel which in later years is called the Kocher incision
- 1899 Oswald attempts to chemically isolate the thyroid principle
- 1900 Vassale and Generali elucidate the function of the parathyroid glands and described postoperative tetany
- 1907 Erdheim the pathologist, associates parathyroid tumors with skeletal decalcification
- 1908 MacCallum shows that tetany in parathyroidectomized dogs is due to a lowered blood calcium
- 1909 Emil Kocher receives the Nobel Prize for medicine. At this time he had operated upon more than 11,000 patients. His mortality was less than one half of 1%.

2

Anatomy and Physiology of the Thyroid Gland

Brief Anatomic Review of the Thyroid Gland

THE THYROID is the largest ductless gland of the endocrine system in the human body. It is situated below the thyroid cartilage frequently referred to as Adam's apple in front of the neck. From an anatomical viewpoint it consists of two lateral lobes each of approximately equal size and shape flat in character and simulating the general configuration of a Brazil nut. The lobes are commonly referred to as the right and the left one of each lies on either side of the upper part of the trachea. A rather narrow band of thyroid tissue connects these two lobes and this band is commonly called the isthmus of the thyroid. The isthmus lies across the trachea covering the second third and fourth cartilaginous rings of the trachea. There is an additional lobe called the pyramidal lobe in about 50 per cent of the individuals. It is also referred to as the pyramid of Lalouette. The pyramidal lobe arises from the upper border of the isthmus and runs in a long narrow strap like process superiorly toward the hyoid bone. When the thyroid is viewed anteriorly the entire gland roughly simulates the letter U. The weight of the normal human thyroid gland varies in the adult male from 20 to 60 gr. It is somewhat heavier in the adult woman.

There are two types of tissue substance which compose the glandular structure namely the essential secretory elements known as the parenchyma and the fibrous connective tissue which encapsulates these elements and in reality is the supporting framework of the gland itself. The functional tissue or the parenchyma consists of numerous very small rounded chambers which have been given various terminologies. These chambers are commonly described as follicles vesicles acini or alveoli. Each of the oval chambers has an interior lining composed of a single layer of epithelial cells. They are filled with a viscid fluid called the colloid which contains the active secretion of the gland. The lobules are independent units which secrete individually and are separated from each other by fine strands of connective tissue. Minute capillary blood vessels which can be found in the strands transport the glandular secretion.

- 1944 Oliver Cope of Boston describes the Delphian node associated with thyroid cancer
- 1946 Radioactive Iodine is prepared at the Atomic Research Plant at Oak Ridge, Tennessee and is made available to the medical profession for diagnosis and treatment of thyroid disease
- 1951 J. Gross and Leblanc discover a hitherto unidentified iodine-containing compound in human plasma which has been identified as 3,5,3',5'-tetraiodothyronine
- 1953 Gross and Pitt Rivers find that synthetic tetraiodothyronine is active in preventing goiter in thiouracil treated rats and duplicates the effects of thyroxine on body growth kidneys, etc
- 1953 Jaffe reports 80% satisfactory remission in 1,720 recorded cases of hyperthyroidism treated with radioactive iodine
- 1954 Tobey Levitt of London publishes a masterful treatise on the thyroid gland which correlates in one volume the scattered knowledge of thyroid diseases
- 1954 Wilkinson and associates suggest that tetraiodothyronine may be the metabolically active form of the thyroid hormone. This belief gains support from the fact that the compound butyl 4-hydroxy-3,5-diiodobenzoate depresses the biological activity of thyroxine but enhances that of tetraiodothyronine. Since this compound depresses the urinary iodide after the injection of diiodotyrosine and of thyroxine it is postulated that its inhibitory effect on thyroxine is due to a restraining effect on the deiodination process. In turn this restraining effect by retarding the breakdown of tetraiodothyronine extends its period of effective biological action

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into larger vessels enmeshed in the stroma. From these vessels the thyroid secretion is poured into the major blood vessels.

If a section of the normal thyroid gland is placed under a microscope there is immediately seen an arrangement of follicles which vary considerably in size. This size may be anywhere from one millimeter in diameter to the smallest visible follicle of about 20 microns. The epithelial cells lining the follicles are cuboidal in shape, each having a round nucleus with



FIG 1 The thyroid gland is a highly vascular organ situated at the front and sides of the neck. It consists of a right and left lobe connected in the central areas by a narrow portion called the isthmus. A pyramidal lobe is present occasionally and arises from the upper part of the isthmus or from either lobe. The thyroid gland overlies the upper trachea and rests close to the inferior borders of the thyroid cartilage and some of the extrinsic muscles of the larynx.

a well marked nucleolus. These cells contain filamentous processes (mitochondria) situated at the inner edge of the cells near the colloid containing lumen. The filamentous processes are considered by some investigators as indicators of cellular glandular activity. They are conspicuous during the active secreting phase and are seen with difficulty when the gland is quiescent. When the thyroid gland functions normally, almost all the follicles contain colloid which is densely packed within the lumen. It is common to see under the microscope small colloid free vacuoles in the thyroid gland which are more marked at the periphery of the colloid mass. Very often this is most noted opposite the free surfaces of individual epithelial cells.

Physiology of the Thyroid Gland

The thyroid gland is not essential as a physiologic organ but it is necessary for the maintenance of health. Its active hormone is called thyroxine (tetraiodothyronine). Thyroxine appears to be the active group of iodo-

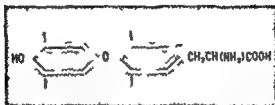


FIG 2 Structural formula of thyroxine. When thyroxine was identified chemically it then became necessary to synthesize it in the laboratory. In 1926 this was accomplished and the structural formula was clearly identified and demonstrated. (Courtesy of Warner-Chilcott Laboratories.)



FIG 3 Crystalline form of thyroxine. This photomicrograph of synthetic L-thyroxine is magnified three hundred times (300 X). (Courtesy of Warner-Chilcott Laboratories.)

thyroglobulin which is considered by many physiologists to be the true thyroid autocoid; however, since thyroxine is the active element, it is acknowledged to be the thyroid hormone. When thyroid extract is given to an experimental animal or to a human being, it is taken up by the thyroid gland, stored there, and firmly bound therein. This is an immediate process.

Under physiologic activity the function of the thyroid gland is to manufacture thyroxine. Thyroxine in turn has the function of maintaining the metabolic rate. By means of its varied activity it alters the metabolism

into larger vessels embedded in thestroma. From the capillary the thyroid secretion is poured into the major blood vessel.

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Physiology of the Thyroid Gland

The thyroid gland is not essential as a physiologic organ for the maintenance of health. Its active hormone (tetraiodothyronine) Thyroxine appears to be the



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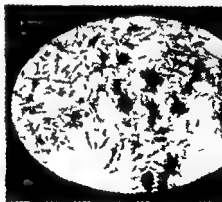


FIG. 3 Crystalline form of thyroxine. This (photomicrograph of thyroxine is magnified three hundred times (300 X). (Courtesy of Warner-Chilcott Laboratories.)

thyroglobulin which is considered by many physicians as a thyroid autoantibody, however, since thyroxine is the hormone acknowledged to be the thyroid hormone. When it is administered to an experimental animal or to a human being, it

in accordance with the changing body physiology. Iodothyroglobulin (through its active chemical group, thyroxin) accelerates the oxidation of proteins, fats and carbohydrates. It also increases the elimination of calcium and magnesium. Thyroxin acts directly on the cardiac muscle to produce tachycardia. Tachycardia continues even after thyroxin ceases to be administered and stops only after the effect of the hormone has been dissipated. Experimentally, a thyroxin stimulated rabbit's heart continues to have tachycardia for several hours even after the heart has been placed in Ringer Locke solution.

A diminution in thyroid secretion due either to inadequate iodine intake or partial thyroidectomy results in a compensatory hypertrophy of the gland. The immediate causative factor for this hypertrophy is the antuitary thyrotrophic hormone from the pituitary gland. Parenteral injection of the antuitary thyrotrophic hormone will produce a compensatory hypertrophy similar in character to that seen in the thyroid remnant following partial thyroidectomy. The thyroid and antuitary glands are intrinsically allied to each other.

When there is an insufficient systemic thyroid hormone the antuitary is stimulated to manufacture more thyrotrophic hormone in order to replenish the deficit. When an adequate quantity of circulating thyroid hormone is produced the antuitary is inhibited and the thyrotrophic hormone is no longer produced to stimulate the thyroid gland. In the etiology of toxic goiter both thyroxin and thyrotrophic hormone plus all those factors which affect these hormones must be considered and evaluated.

Exophthalmic goiter and goiter without exophthalmos are the results of excessive secretion of antuitary thyrotrophic hormone. In exophthalmic goiter the antuitary is stimulated by an unknown factor. In hyperthyroidism without exophthalmos the antuitary is overactive because there is an insufficient thyroid secretion so that the inhibiting mechanism blocking the secretion of the thyrotrophic hormone is not available. Irrespective of the innumerable theories advanced in the etiologic discussions on hyperthyroidism one factor always remains. This factor is the antuitary thyrotrophic hormone, the indispensable agent which produces the increase in thyroid gland activity.

The destination or end point of the thyrotrophic hormone is the parenchyma of the thyroid gland. When this hormone arrives at the thyroid gland certain things take place. What exactly occurs is not definitely known, however, there is available a certain amount of evidence which leads one to suppose or presuppose what does happen. This activity is more easily interpreted if one thinks in terms of what is actually known of the thyroid gland functions. These functions concern themselves with the manufacture of the thyroid hormone and are identified as

- 1 A mechanism for trapping iodide from the blood stream
- 2 The synthesis of thyroxine which involves the iodination of tyrosine to diiodotyrosine and the coupling of two molecules of the latter to form thyroxine. The reactions take place within the chain molecule of thyroid protein called thyroglobulin
- 3 The storage of the hormone as thyroglobulin within the thyroid follicles
- 4 The discharge of the hormone into the body itself via the blood stream

A study of the action of the thyrotrophic hormone is facilitated by the fact that certain drugs are available which are capable of separating the several thyroid functions. Potassium ulfoacetate blocks the trapping mechanism. Another drug which can do this is perchlorate and certain other ions. Thiouracil and other drugs of this family interrupt the synthetic mechanism. Thyrotrophic hormone probably promotes all the functions of the thyroid but when only a part is blocked it will accelerate the unblocked thyroid physiology. Thus the gland blocked with thiouracil will still trap iodine when the thyrotrophic hormone is administered. It will also liberate the hormone. In view of the fact that the synthetic mechanism is blocked this must indicate that thyrotrophic hormone promotes the breakdown of stored thyroglobulin. The physiological release of the hormone may be the earliest effect of thyrotrophic hormone on the thyroid gland. Investigative work of Dr. Robertis suggests that this release is due to almost immediate activity of the proteolytic enzyme system of the thyroid gland.¹⁰ This immediate activity brings about a reduction in the molecular size of the stored protein and permits the thyroxine containing fractions to escape into the circulation. Hypertrophy and hyperplasia of the thyroid parenchyma then occurs with an increased trapping of iodine. Finally 48 hours or more after the injection of thyrotrophic hormone an increased synthesis of the hormone results.

It may be well to ask what the thyroid gland itself does to thyrotrophic hormone while the above activities are taking place. Rawson and his associates have shown that when thyrotrophic hormone acts on the thyroid gland it (thyrotrophic hormone) disappears.^{11, 12} This disappearance however is not due to destruction because hormone activity can be restored by heat or by certain mild reducing agents. The hormone is merely inactivated but retains its capability of reactivation. The hormone may be found in the urine in its inactivated form and under certain circumstances it has been found in its active form as well.

The close relationship between the pituitary and thyroid glands has been spoken of as the *Pituitary Thyroid Axis*. This term first employed

Biochemistry of the Thyroid Gland

The synthesis of the thyroid hormone has been discussed rather briefly in previous paragraphs. Specifically, it must be recalled that, in 1944 Harington actually formulated the various steps of thyroid hormonal synthesis *in vivo*.⁶ These steps are

- 1 Concentration of iodide in the thyroid gland
- 2 The oxidation of iodide into iodine
- 3 The iodination of tyrosine to diiodotyrosine
- 4 The coupling of two diiodotyrosine molecules to form thyroxine

A more recent work (Gross and Pitt Rivers) has identified a new iodinated amino acid as a normal constituent of human plasma and of the thyroid gland.³³ This new amino acid (3,5,3'-triiodothyronine) is more active than L-thyroxine in preventing thiouracil induced goiter in rats. It is at least as active as L-thyroxine in restoring the basal metabolic rate and blood cholesterol of myxedematous patients to normal levels (1952). These findings lead to the consideration of a further step in the synthesis of the thyroid hormone. To the previously mentioned four steps one should now add the fifth

- 5 The formation of triiodothyronine

It is possible that triiodothyronine may be formed by enzymic dehalogenation in the thyroid as well as in other tissues. It must be remembered that the amount of triiodothyronine present in the thyroid gland is very small compared with the amount of thyroxine in the gland. It is therefore possible that more sensitive methods for the detection of dehalogenation are required than have been used previously. The entire question of the biosynthesis of triiodothyronine is not settled at this time.

Hydrolysis of Thyroglobulin in the Thyroid Gland

It has been mentioned previously that the thyroid gland possesses a proteolytic enzyme. This enzyme can be demonstrated in the follicular colloid extracted from the thyroid gland of experimental animals. The proteolytic activity of this enzyme can be increased after the administration of thyrotrophic hormone. Similarly it can be decreased following the administration of iodine. This enzyme activity varies in different pathological conditions in humans. In patients with severe toxic goiter, it is increased to twice the normal activity. In patients with simple colloid goiter it is lowered.

Gross and his associates have shown that the thyroid contained small amounts of free iodinated amino acids which could be extracted with butanol from the thyroid gland without previous hydrolysis. These free iodinated amino acids have been identified as

- 1 Monoiodotyrosine
- 2 Diiodotyrosine
- 3 Thyroxine
- 4 Triiodothyronine

The α are presumably formed by proteolysis of thyroglobulin

In reference to monoiodotyrosine and diiodotyrosine neither one of the α amino acids have been found in the circulation. In 1931 investigators demonstrated that the thyroid gland possessed an enzyme system which was able to dehalogenate both mono- and diiodotyrosine.¹⁷ It was further found that the dehalogenase was not inactive towards the iodinated tyrosines when they were bound in thyroglobulin. Therefore only free amino acids could be attacked by the enzyme dehalogenase. The metabolism of the iodinated tyrosines therefore can be regarded as taking place entirely within the thyroid gland after proteolysis from thyroglobulin. They are completely dehalogenated and the iodide formed can be utilized again for the cycle of thyroid hormone synthesis. Furthermore it has been shown that the activity of the enzyme is not destroyed with the destruction of the thyroid cell and thyroid extracts have been found to be active. It appears that this particular enzyme is active only on halogenotyrosine.

Circulating Thyroid Hormone

The fate of thyroxine and triiodothyronine after their proteolytic release from thyroglobulin has been the topic of much speculation. The question advanced was whether the circulating thyroid hormone was a simple amino acid, a peptide or a polypeptide of thyroxine or thyroglobulin itself. In 1948 Taurog and Chirikoff (quoted by Gross) produced a large amount of evidence substantiating the contention that the plasma hormone was thyroxine. This work received confirmation by others (e.g. Laidlaw) and it became generally accepted that thyroxine alone was the circulating hormone.

Our present knowledge of the high thyroidal activity of triiodothyronine requires that it should be called the thyroid hormone. The sequence of events leading to the appearance of the hormone in the blood can be outlined as follows:

- 1 Synthesis of thyroxine and triiodothyronine in the thyroid (either simultaneously or consecutively)
- 2 Liberation of thyroxine and triiodothyronine from thyroglobulin by proteolytic hydrolysis
- 3 Passage of thyroxine and triiodothyronine from the thyroid into the circulation

It cannot definitely be stated whether thyroxine is the precursor of tri-

iodothyronine in the thyroid gland and is itself physiologically inactive, or whether both compounds possess independent activity in their relation to each other. Until the sequence of events leading to their synthesis in the thyroid gland and their respective activities on the structures outside of the thyroid gland are more accurately understood the regulating thyroid hormone may be regarded as composed of both of them.

Summary of Recent Knowledge of Biochemistry of the Thyroid Gland

1 The three main biochemical functions of the thyroid gland are

- (a) The collection of iodide from the plasma
- (b) The transformation of iodide into organically bound iodine
- (c) The release of the hormone into the circulation

2 There are various factors controlling the synthesis of the thyroid hormone and experimental evidence has been accumulated substantiating the nature of this synthesis to be enzymatic or a simple chemical reaction.

3 The pituitary gland exerts a powerful influence in the synthesis of the thyroid hormone. Recent evidence has been offered on the independent action of thyrotropin on the iodide concentrating mechanism and the organic binding of iodine.³³ There is conflicting evidence as to whether the pituitary actually controls the organic fixation of iodine or merely accelerates the reactions involved in this process.

4 As to the fate of iodinated amino acids in the thyroid it is believed at present that monoiodotyrosine and diiodotyrosine do not leave the thyroid gland after proteolytic hydrolysis of thyroglobulin but are enzymically deiodinated with the formation of iodine. This iodide is available for reutilization in hormonal synthesis. Thyroxine and triiodothyronine are released into the circulation.

5 Attention is called to 3,5,3 triiodothyronine in thyroid hormone action. Triiodothyronine exhibits perhaps greater hormonal activity than thyroxine and can be shown to be derived from thyroxine in the extra-thyroidal tissues. It has not been definitely established whether hormonal activity is shown by thyroxine itself or whether its entire effect is due to its conversion into triiodothyronine. Both substances are present simultaneously in the circulation and tissues (Gross and Pitt Rivers).³³

Although all the answers are not known modern investigators are attempting to unravel the physiological conundrum of hyperthyroidism. Each year witnesses the unveiling of newer knowledge which brings the physician and surgeon closer to the solution of thyroid diseases.

3

The Clinical Picture of Hyperthyroidism

PRIMARY HYPERTHYROIDISM is a term employed to designate toxic goiter also often called Graves disease Basedow's disease Flajani's disease or diffuse toxic goiter Hyperthyroidism may also result from adenomatous colloid goiter or cancer in the thyroid gland In the e instances it is proper to employ the term "secondary hyperthyroidism" e.g. adenomatous goiter with secondary hyperthyroidism A patient having any one of the e types of hyperthyroidism (usually a female patient since hyperthyroidism occurs much more frequently in women than men) may present herself to the doctor either because of toxic symptoms or because she has noted a mass in her neck The clinical symptoms of thyroid toxicity are reviewed under figure 4

One of the significant aspects of hyperthyroidism is that it is a manifestation of a constitutional disorder Hence the dictum "once a hyperthyroid patient always a hyperthyroid patient" The thyroid enlargement itself is merely an outward sign of a hidden underlying constitutional disturbance with many ramifications

Thyroid enlargement is not of itself a serious or a death producing situation It is true however that it may be disfiguring and makes the individual self-conscious because of a mass in the neck Thyroid enlargement in advanced cases of goiter does produce tracheal compression or discomfort due to pressure in the neck This so disturbs the patient that she may demand an operation for relief of pressure symptom The e local signs and visible distress are insignificant when compared to the systemic disturbed physiology underlying hyperthyroidism In figure 4 the various organs affected by excessive thyroid function are graphically illustrated

It is proper therefore to define primary hyperthyroidism as a wide-spread complex constitutional disorder (endocrinopathy) involving the thyroid other endocrine glands the tissues of the orbit the spleen the thymus the lymphatic reticuloendothelial hemopoietic muscular nervous and almost all other systems in the human body The cause for these underlying disturbances is not fully understood so that the exact etiological cause of primary hyperthyroidism has not been definitely established

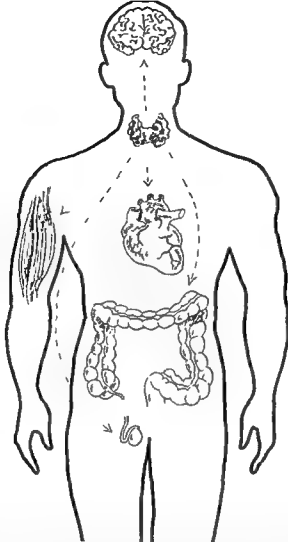


FIG 4 Spheres of influence attributed to the thyroid gland. In addition to its metabolic function, the thyroid gland takes an active part in maintaining the normal conditional balance of the neuromuscular, circulatory, digestive and reproductive systems. This function is made manifest on the systems from the clinical picture resulting from the extremes of hypofunction (myxedema) and hyperfunction (hyperthyroidism) of the thyroid gland.

Typical of myxedema are flabby, hypotonic muscle, sluggish circulation, bradycardia, menstrual disorders and sterility, dry, coarse skin and constipation. In hyperthyroidism, the muscular changes range from mild myasthenia to severe atrophy. Tachycardia is common; amenorrhea or oligomenorrhea is frequent. Like the diminished intestinal peristalsis of myxedema, the profuse sweating of hyperthyroidism is probably due in part to the action of the thyroid on the vegetative nervous system. The effect on the central nervous system is even more pronounced and remarkable. The thyroid hormone shortens the reaction time of the nerves and heightens their irritability. Extreme toxic hyperthyroidism is characterized by emotional instability, hyperexcitable nervousness, tremor, crying without cause and confused thinking. The personality itself may undergo many changes. Fatigability or rapid tiring is a characteristic symptom of hyperthyroidism. Physical endurance and stamina are usually reduced in the patient with excessive thyroid function. (Adapted from an

Signs and Symptoms of Hyperthyroidism

As has been stated toxic goiter (thyrotoxicosis) means a symptom complex which not only produces thyroid enlargement but results in palpitation rapid pulse tremor irritability crying without cause and associated loss of weight (emaciation) due to an increased rate of nitrogenous and glycosuric metabolism. The above symptoms may be listed as characteristic expressions of excessive or hyperthyroid activity.

There are two forms of toxic goiter namely primary and secondary. In the primary type toxic signs and symptoms associated with a simultaneous enlargement of the thyroid seem to occur in an individual with a previously healthy thyroid gland. It is usually of sudden onset with

TABLE 1 *Thyrotoxicosis Primary and Secondary Toxic Goiter*

| Primary Thyroid | Secondary Thyrotoxicosis |
|--|--|
| Affects a previously healthy gland | Affects previous goiter bearers only |
| Onset sudden and progresses rapid | Onset gradual and course chronic |
| Exophthalmos common and often severe | Exophthalmos rare and usually slight |
| Nervous phenomena prominent | Nervous phenomena slight or absent |
| Basal metabolic rate very high | Basal metabolic rate moderately high |
| Cardiac symptoms may be conspicuous until later stages | Cardiac symptoms prominent early marked auricular fibrillation |
| Goiter diffusely hyperplastic firm and small | Goiter usually nodular and large |
| Response to iodine medication often dramatic | Iodine medication often beneficial but less striking in effect |

rapid progression and quite often is associated with protrusion of the eyes (exophthalmos) hence the term exophthalmic goiter (Graves disease or Parry's disease).

The secondary type of hyperthyroidism usually arises in patients in whom simple goiter (sometimes called parenchymatous colloid or nodular goiter) has existed previously for some time usually one or more years. The onset of this type of hyperthyroidism is rather insidious and protrusion of the eyes is uncommon. When exophthalmos does occur it is usually not very marked.

From an etiological point of view there does not appear to be any relationship between the toxic goiters and the simple goiters. The toxic types are not associated with environmental iodine deficiency. As far as our knowledge enlightens us at the present time it does not appear that their distribution has any relationship to the geographical occurrence of endemic goiter. In toxic goiters there is no doubt however that a derange-

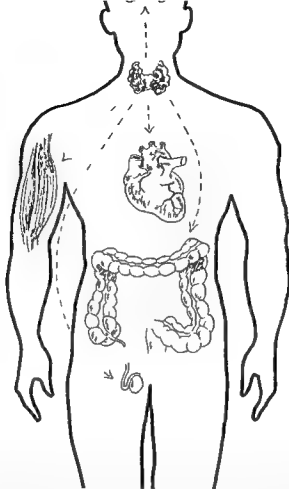


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shock illness or infection. It is not an unusual story in the case history of an individual with exophthalmic goiter, to have the patient definitely equate the onset of symptoms with a shocking experience—for example the sudden death of a parent or relative, a motor accident, financial tragedy, divorce or marital disturbance. Other patients may present a history of a prolonged emotional anxiety such as studying for examinations or preparing for the legal, medical or engineering professions. Some thyroid patients will definitely establish the time of the toxic symptoms with an attack of a virus infection, a common cold or similar infective process.

What actually happens within the thyroid gland due to the emotional or infective processes is of much theoretical speculation. It can be stated however that the thyroid gland under the stress and strains previously mentioned has an exaggerated and uncontrolled secretory activity. It continuously eliminates the thyroid hormone in large quantities so far in excess of what the human body requires that all the toxic symptoms of hyperthyroidism result. This excessive elimination of thyroid hormone was called thyroid diarrhea by Kocher.¹⁴⁶ The chemical alterations and the histological changes which take place in the gland of exophthalmic goiter (Graves disease) are most satisfactorily discussed by Harrington in his classical textbook on the thyroid gland mentioned under physiology.⁹

It is an established fact that insufficient supplies of iodine cause certain changes in the thyroid gland. The changes result in goiter. Characteristic glandular changes in goiter may be recognized under the microscope. To fully understand the architectural alteration in the thyroid gland the histological structure of the thyroid should be known.

The first thyroid alteration is due to iodine insufficiency and can be seen (under the microscope) in the epithelial cells lining the acinus. The cells change from a flat or low cuboidal form to long columns. High columnar epithelium is never seen in a normal thyroid gland. In association with this hypertrophy of cells is a marked drop in the iodine content of the gland itself. This is demonstrated by the diminution in the amount of colloid which absorbs the stain. This colloid becomes rarified and filled with vacuoles. Associated with this is an increased vascularity. Microscopically this is demonstrated by tortuous engorged and congested blood vessels. In addition the microscope reveals the formation of new vessels within the connective tissue. With the prolonged deprivation of iodine the thyroid gland will show hyperplasia characterized by an excessive multiplication of the cells comprising the follicular epithelium. In addition there is a disappearance of the colloid fluid which becomes more marked as the hyperplastic process advances. When the hyperplastic process becomes intense the epithelial lining folds over itself so that it may even fill

ment of iodine metabolism does exist. It must also be remembered that there would be no secondary toxic hyperthyroid patients if the individuals did not have simple non-toxic goiters to start with.

Exophthalmic Goiter (Primary Hyperthyroidism, Graves Disease)

The first case of exophthalmic goiter was recorded in medical literature by Caleb Hillier Parry (1755-1822).¹⁴⁶⁻⁹ His description of this disease was: 'There is one malady which I have in 5 cases seen coincident with what appeared to be enlargement of the heart, and which so far as I know has not been noticed in that connection by medical writers. The malady to which I allude is enlargement of the thyroid gland.' Parry's observation was made in 1786 and all students of medical history agree that if anyone's name deserves to be attached to the disease it should be Parry's. However, this syndrome has been known as Graves disease in England and the United States and as Basedow's disease in continental Europe. The use of these proper names still persists in spite of the fact that Graves' description was less accurate than Parry's and was made much later (in 1835 to be exact). Dr Basedow's presentation of this disease, although it was more complete, did not appear until 1840.¹⁴⁶ In Italy, primary hyperthyroidism is called Flajani's disease in honor of an Italian physician who described the disease in 1800.¹⁴⁶

Etiology of Hyperthyroidism

Under the discussion of thyroid physiology several facts were presented which intimated that etiological agents when acting in a disturbed fashion may result in hyperthyroidism. The exact mechanism cannot be stated and proven didactically. However, clinical experience and laboratory experimentation have brought forth certain aspects of this disease which should be considered in its etiology. For example, clinical studies definitely establish that exophthalmic goiter is much more common in women than in men; that fair-haired and fair-complexioned women fall victims to this disease more than dark-haired and dark-complexioned women. Exophthalmic goiter is not commonly seen before 15 and is infrequently encountered after 50 years of age. It seems to be much more frequent in persons who do mental work than in those who do manual labor. Exophthalmic goiter produces in women an artificial vivacity and temperament which label some of them 'the life of the party.'

In the etiology of this disease one may also state that some patients undoubtedly have inherited a nervous mechanism which is not very stable and which may predispose them to hyperthyroidism. In such individuals, however, the immediate cause for the disease may be a serious emotional

pla is it does not return to an exact anatomic normal state. Because of the changes the colloid goiter is the nearest approximation to the normal both from an anatomic and physicochemical point of view. Functionally the colloid gland is able to perform all the reactions which are exhibited by a normal thyroid gland. David Marine of Montefiore Hospital, New York, has shown that the hyperplastic process subsequent to iodine deficiency may develop from a colloid gland but is in exactly the same way as it does in a normal thyroid gland.¹⁶² Thus the resting goiter (colloid gland) will again go through the same cycle of changes whenever the iodine deficiency which originally caused the colloid goiter is renewed.

In summary, therefore, it may be stated that the developmental stage of a primary hyperplasia that is one arising on a normal gland but is marked by a drop in the iodine store, a decrease in colloid substance, proliferation of the epithelial cells which change from low cuboidal to columnar and a larger and softer gland. In the involutionary or physiological recovery stage which may occur spontaneously or may be hastened by iodine administration and is the usual mode of termination of an active hyperplasia the gland becomes firmer, a greater amount of denser and intensely staining colloid accumulates in the follicles, high columnar epithelium returns to the normal columnar type, and there is an increase in the iodine store. Atrophy or the state of physiological exhaustion is less common but is seen in the myxedema of children and following acute hyperplasia of young adults. Here the colloid is very markedly reduced or absent and the follicles are obliterated by cell death. The stages of a secondary hyperplasia that is one developing on a colloid gland but is essentially different from those arising in a normal gland.

Colloidophagy in the Thyroid Gland

In 1940 Japanese investigators were among the first to call attention to the fact that the colloid of the normal thyroid gland contained certain cells which had the appearance of monocytes.¹⁶³ Three years later colloidophagy in chronic thyroiditis was described by Buno.¹⁶⁶

Prior to this time Loeb and Basset mentioned macrophages in the thyroid follicles of animals.¹⁶⁴ They believed that colloid reorption by phagocytes plays a significant part in the normal removal of colloid. After injection of thyrotropic hormone in lizards, Eggert saw wandering cells enter the hyperactive follicles, ingest colloid, and carry it into blood vessels.¹⁶⁵ Williams implanted transparent chambered thyroid tissue into rabbit ears and observed in the living tissue macrophages entering follicle. Thyrotropic hormone increased the activity of these colloidophages. There was no evidence of degeneration of the epithelial wall of the invaded follicles.¹⁶⁴ Williams believed that some special chemical alteration of the colloid stim-

the acinus space excluding colloid completely. As a result the entire gland may eventually become a solid mass of functionless cellular tissue. With the progression of hypertrophy and hyperplasia the gland becomes more visibly enlarged. If it becomes truly extensive, the abnormal development becomes quite visible in the neck.

If the iodine deficiency which has stimulated the hyperplasia becomes so severe that the degenerative process continues, then the thyroid gland,

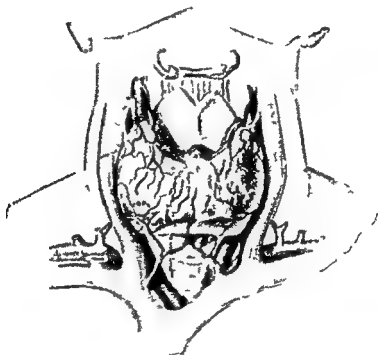


FIG. 5 Anatomy of diffuse toxic goiter (primary hyperthyroidism or Graves disease) (Reprinted from Pfizer *Spectrum* appearing in the J. A. M. A.)

not able to meet this stress and strain will eventually become completely exhausted and atrophied. Such a state may be associated with myxedema. Conversely, the iodine deficiency may be temporary and the thyroid gland may be able to tolerate the transient deprivation until iodine is administered again or until the physiological stimulus which has resulted in the unusual demands on the thyroid has been eliminated. When this occurs and the stimulus is removed the excessive secretory activity ceases, the hyperplasia no longer takes place and involution occurs with the thyroid gland returning to a quiet state.

It is well to recall that once the thyroid gland has undergone hyper

from the pituitary gland. The stimulated cells react by producing a metabolic activating thyroid hormone. This hormone normally inhibits overproduction of thyrotropin by means of a delicately sensitive auto-balancing mechanism. By means of histological section and measurements can be determined which categorize the type of epithelial alteration into the six progressive phases of the toxic thyroid gland.

- 1 Epithelial hyperplasia
- 2 Lympho epithelial hyperplasia
- 3 Focal lymphoid hyperplasia
- 4 Diffuse lymphoid hyperplasia
- 5 Fibrolymphoid hyperplasia
- 6 Fibrosis

The degree of toxicity is usually divided into three parts namely mild, moderate and severe.

According to LeVitt most of the patients studied varied between moderate and severe degree of toxicity in the epithelial hyperplasia phase. The lympho epithelial hyperplasia phase showed a mild degree of toxicity in 24 per cent and severe toxicity in 30 per cent of the patients studied.

In focal lymphoid hyperplasia the incidence of mild toxicity was 25 per cent moderate toxicity was 36 per cent and severe toxicity was found in 28 per cent of the patients studied. Diffuse lymphoid hyperplasia patients generally displayed mild and moderate toxicity similar to the focal lymphoid group with severe toxicity falling to 21 per cent.

Fibrolymphoid hyperplasia (Hashimoto's disease) patients showed mild toxicity in 60 per cent and moderate toxicity in 33 per cent of patients. The fibrosis (Riedel's struma) was found in patients over 40 years of age. None had any specific history of any preceding severe thyrotoxicosis.

Methods for Determining Thyroid Function

Many physicians and surgeons have overemphasized the basal metabolic rate as a criterion for arriving at a diagnosis of hyperthyroidism. Thyroid surgeons have learned to rely on the pulse rate and its stabilization *under treatment as a more reliable criterion for toxicity and operability*. An elevated pulse which has fallen and has been maintained at a plateau level indicates a satisfactory response to therapy and suggests to the surgeon that thyroidectomy may be performed. This is true even if the basal metabolic rate remains elevated. Faulty recordings of the basal metabolic rate may result from technical inaccuracies and the failure to secure the patient's full cooperation. Therefore this method of evaluation should not be relied upon entirely.

ulates the entry of macrophages into thyroid follicle but did not suggest the nature of this chemotactic substance. Several observations suggest that thyrotropic hormone increases the content of the thyroid in phospholipid. Morton and Schwartz demonstrated in vitro that phospholipid increased markedly in supravital thyroid tissue after adding thyrotropin.¹⁶ Dobyns found a large number of lipid droplets in the thyroid epithelium of guinea pigs after injection of thyrotropin (Antuitrin T). Ferguson injected subcutaneous lipid extracts from thyroid colloid into guinea pig and saw histiocytes, giant cells, and lymphocytes attracted by the injected lipid.¹⁶ In the colloid and interfollicular tissue of positive cases macrophages were found with granules that stained black with sudan black B.^{164, 165, 166, 167}

In 16.2 per cent of thyroids obtained by autopsy macrophages were found in the lumen of follicles. The involved follicles were surrounded by lymphocytes. There was no relationship between the presence of colloidophages and cause of death. Women 50 years or older predominated in positive cases.¹⁶ In 49 of 75 surgical goiters colloidophages were noticed. They were present not only within the follicle lumen but also in the follicle wall, the center of lymph follicles, and in the interfollicular tissue. Exophthalmic goiters and thyroids with chronic thyroiditis were most frequently represented in positive findings.¹⁶⁴ This new study of the etiology of the thyroid gland may be of future value in studying thyroid activity and neoplastic diseases of the gland.

Thyroid Disturbances in Terms of the Matrical Theory

DeCoursey of Ohio has brought attention to the matrical theory as applied to the thyroid gland.^{345, 491} The matrical theory was presented first to explain the origin of cancer as a disease of the matrix. Its application to the thyroid gland brings forth the hope that a new interpretation may be used to evaluate the mysteries of the diseases of this gland. It may therefore become evident that the concept of a transcendent dynamically integrated matrix may be used to construct the basis for an entire new concept in the disturbed human physiopathology. The exact status of the matrical theory in thyroid disease cannot be evaluated at the present time. However, future studies may bring light on the development of certain thyroid diseases. The specific diseases in question are arteriosclerosis of the thyroid as well as benign and malignant tumors of the gland.

T. Levitt of London in his masterfully composed textbook postulates six progressive phases of the toxic thyroid gland.¹⁴ His postulates are based upon the alteration of epithelial tissue. He believes as do many others that the epithelial cell is the true center of thyroid function. It is this basic cell which is altered due to the thyrotropic hormone arising

tests shows that the basal metabolism test is of limited value in the diagnosis of thyroid function²⁴⁴

1 New and Simple Test for Hyperthyroidism Employing I-Triiodothyronine and the 24 Hour I^{131} Uptake Method

The administration of thyroid thyroxine or triiodothyronine causes a sharp reduction in I^{131} uptake by the thyroid in euthyroid subjects but little if any change in Graves disease. This distinction is so clear cut that an investigation was undertaken by Werner and Spooner to establish whether the reaction would be as useful diagnostically as the results implied. Since thyroid contains iodides and several organic iodinated compounds which might induce false positive results and since the effects of thyroid and of thyroxine are protracted after treatment is discontinued crystalline triiodothyronine was chosen as the test agent. The material is available in pure form and has a more rapid half life within the body than thyroxine. While this study was being pursued Græber independently was investigating the use of thyroid for the same purpose and obtained similar results as Werner and Spooner.²⁴⁵

Summary of this Test for Hyperthyroidism

1 Triiodothyronine 75 or 150 μ g daily by mouth for 8 days caused a sharp decrease in the twenty four hour I^{131} uptake in 48 euthyroid patients without thyroid disease so that no value exceeded 20 per cent. In contrast no value under 35 per cent was obtained in patients with toxic goiter following triiodothyronine administration. Side effects occurred in euthyroid patients only with a dosage of 150 μ g and were relatively minor.

2 About a third of the euthyroid patients in this series had initial 24 hour I^{131} uptake values in excess of 40 per cent and a third of the hyperthyroid patients had uptakes less than 50 per cent. Triiodothyronine was virtually specific in clarifying the diagnosis in this group with overlapping values.

3 Triiodothyronine was valuable in establishing the activity of the eye complications of Graves disease. Euthyroid patient with the early eye signs of Graves disease and patients with overt hyperthyroidism showed an abnormal response to triiodothyronine but patients in sustained remission reacted normally.

4 Patients with nontoxic diffuse goiter responded like normal subjects to the administration of triiodothyronine whereas 5 of the 21 patients studied with nontoxic nodular goiter had no response to triiodothyronine administration even though the initial uptake values were within the

In addition to the indirect calorimetry or oxygen consumption test other methods are used in the evaluation of the patient with thyroid disease. These are

- 1 Serum cholesterol level
- 2 Radioactive iodine uptake
- 3 Blood protein bound iodine level
- 4 The McWhirter Freibrun metabolic calculator

The latter method is a device that utilizes available information (e.g. body weight, blood pressure and pulse rate) from which the basal metabolic rate is determined by a standard formula. Of these various methods only oxygen consumption, serum cholesterol determination and the use of the metabolic calculator are suitable for the doctor in his office.¹⁰⁰

The measurement of the concentration of radioiodine (I^{131}) in the thyroid gland and the chemical determination of the protein bound iodine of the blood serum are laboratory tests that have gained increasing use in the diagnosis of thyroid disease. A brief comparison between the two methods, namely, radioiodine and protein bound iodine determination and the contrast of these tests with the determination of the basal metabolic rate is made here. By means of the Geiger counter the concentration of the radioiodine in the thyroid gland is measured one hour and 24 hours after the oral administration of $10 \mu\text{c}$ of I^{131} . The patient is in a fasting state to facilitate the one hour determinations of radioiodine. A careful history of any previous intake of thyroid extract, iodine medication, iodized salt or iodized oils as used in x-ray diagnosis is obtained to rule out any errors from these sources. Six cubic centimeters of blood are drawn into a tube and the protein bound iodine is determined by the method of Brown. This method enables the technician to make up to 12 duplicate determinations daily. The same iodine compounds which interfere with the I^{131} tests adversely affect the determination of protein bound iodine. The I^{131} and protein bound iodine tests performed in 50 euthyroid and in 25 hyperthyroid patients revealed that in normal patients more than 97 per cent of the results were between the limits of 5 per cent and 45 per cent I^{131} concentration. One hundred per cent were between 3.5 and 8 per cent protein bound iodine gamma per 100 cc. of serum. In the hyperthyroid patients I^{131} concentration was between 50 per cent and 85 per cent in over 94 per cent of the patients studied. In all cases the protein bound iodine per 100 cc. of serum was between 8 and 16 or more. Despite the expected overlap between the higher normal and lower hyperthyroid readings there was a clear cut separation between the euthyroid and hyperthyroid group with both tests. This comparison of thyroid function

tions. Found among children only in districts where goiter has been severely and continuously endemic for long period of time. In contrast to sporadic cretinism the endemic type exhibits a wide range of physical and mental defects with many mixed and intermediate varieties. Is notably associated with deaf mutism and cardiac failure. Subcutaneous swellings seen in sporadic cretinism are often absent.

reach a large size. Histologically the follicles are greatly distended and rich in colloid. The percentage iodine content is less than normal but owing to increased use the total may be equal to or greater than normal.

3. Nodular Goiter (Strum. Nodul.)

Commonest form in patients over age of 30 in all endemic areas. Is the result of long continued action of the goiter producing factor working perhaps through generations and intensified by inbreeding. Gland composed of nodular masses (either of parenchymatous or colloid structure) embedded in a dense overgrowth of tough fibrous connective tissue. The nodules may be generalized or localized thus:

- (a) Generalized Multiple Synonyms:
Adenoparenchymatous Goiter
Adenomatous Multiple Adenomatous
Related Goiter
- (b) Localized Single
Colloid Adenoma
Parenchymatous or Follicular
Adenoma of Wollmer
Non-follicular

Affects previous goiter carriers only hence secondary. Onset gradual and course of disease chronic. Pathological rare and usually slight. Nervous phenomena slight or absent. Blood metabolic rate increased + 40 per cent. (outer usually nodular and large exception may be diffusely parenchymatous or colloid in type). Iodine medication often beneficial but not so striking in effect as in primary thyrotoxicosis.

TABLE 2 Classification of Thyroid Disturbances

| Thyroid Disturbances | Age | Sex | Abnormalities | Pathogenesis | Prognosis |
|---|------------------------|--------|------------------------------|--------------------------|------------------------------------|
| Myxedema—Atrophy of Thyroid
Myxedema the classical manifestation of hypothyroidism is characterized by myxedema, mental retardation, depression, headache, cold intolerance, constipation. Since the thyroid is atrophied the condition is non-gonitrous. It occurs in both adults and children. | Adults (Gull & Hirsch) | Female | Atrophy of thyroid gland | Primary hypothyroidism | Chronic, progressive, irreversible |
| Chilren (Sporadic Cretinism)
Associated with atrophy of the thyroid hence non-gonitrous. Usually congenital sporadic cretinism rarely born of gonitrous parents. Mental characteristics are lethargic dull of subnormal temperature round head coarse facial features short scanty hair and skin thickened by subcutaneous gelatinous deposits. Rarely survive to adult life. | Children | Female | Atrophy of thyroid gland | Primary hypothyroidism | Chronic, progressive, irreversible |
| Simple Goiter—Endemic Sporadic
A hypertrophy of the thyroid gland caused by increased need of thyroid secretion. The condition is one of thyroid enlargement only and is unaccompanied by any definite clinical symptoms except perhaps a feeling of tiredness. Hence the term simple or benign goiter. The rate includes Transitory Reversible Types | Adults | Female | Enlargement of thyroid gland | Simple goiter | Chronic, progressive, irreversible |
| Colloid Goiter (Struma Diffusa Colloides)
Is the common type in areas of low endemicity (e.g. England and Wales) develops usually in early life and is rare in typical form after age of 30. The goiter is diffuse, symmetrical, rather soft and may | Adults | Female | Enlargement of thyroid gland | Colloid goiter | Chronic, progressive, irreversible |
| Struma Diffusa Colloides
Is the common type in areas of high endemicity (e.g. Switzerland) seldom seen after puberty. The goiter is diffuse, symmetrical, firm and of small size. Histologically there is extensive hyperplasia of follicles but devoid of colloid. Iodine content always reduced both in percentage and total. | Children | Female | Enlargement of thyroid gland | Struma diffusa colloides | Chronic, progressive, irreversible |
| Struma Nodosa
Is the common type in areas of high endemicity (e.g. Switzerland) seldom seen after puberty. The goiter is diffuse, symmetrical, firm and of small size. Histologically there is extensive hyperplasia of follicles but devoid of colloid. Iodine content always reduced both in percentage and total. | Children | Female | Enlargement of thyroid gland | Struma nodosa | Chronic, progressive, irreversible |
| Struma Nodosa
Is the common type in areas of high endemicity (e.g. Switzerland) seldom seen after puberty. The goiter is diffuse, symmetrical, firm and of small size. Histologically there is extensive hyperplasia of follicles but devoid of colloid. Iodine content always reduced both in percentage and total. | Children | Female | Enlargement of thyroid gland | Struma nodosa | Chronic, progressive, irreversible |

neck lesions are metastases from either primary or secondary pulmonary cancers.

Aspiration of a neck mass has been thought on many occasions to be either a means of biopsy study or for the purpose of injecting an iodized substance for x-ray study. The procedure of aspiration is not recommended for neck masses.

By utilizing the cardinal procedures of inspection, palpation, and auscultation, valuable information becomes readily available. The first revelation is whether the pathology is one mass or multiple masses. If the masses trans-



FIG. 6. Anterior view of a branchial cyst located in the upper carotid triangle of the neck. (Lisendrath: *Surgical Diagnosis Philadelphia*, W. B. Saunders Co., 1937.)

illuminates a cystic tumor must be considered. Compression of the mass suggests its consistency. For example, vascular masses are compressible and esophageal diverticula empty with compression. Deglutition produces motion in masses of thyroid origin. When the tongue protrudes, motion in a neck mass indicates a thyroglossal cyst or fistula (attachment to the base of the tongue). The presence of pulsations may be deceiving for an underlying artery may transmit pulsations. A mass that is immobile from its incoercibility strongly suggests an inflammatory lesion. Fixation of malignant tumors occurs only when the malignancy has infiltrated. A well defined tumor edge that is smooth suggests a benign lesion. Injury to the neck area followed by a rapidly developing mass indicates hemorrhage. Tenderness and heat over the mass suggest inflammatory lesions.

The rate at which a mass may change in size may offer a clue to the etiology of the mass.

normal range. Radioautographs of three of these glands revealed the nodules to be functionally active.

From the results obtained it appears that a new diagnostic method has been added to the armamentarium of the thyroid diagnostician.

Recognition of Neck Masses

When presented with a mass or nodule in the neck, thought must also be given to other causes for a tumor in the neck. As a general statement it may be stated that tumors in the midline of the neck are usually of thyroid origin.

In order to institute proper therapy, any mass in the neck must be identified whenever possible. A mass or masses in the cervical region usually can be evaluated and identified. Exceptions occur in which even the most agacious examiner may err. However, by means of a careful history, physical examination, x-ray and biopsy studies, a satisfactory diagnosis can be made. A proper diagnosis enables the surgeon to decide whether the lesion is amenable to surgical removal or is a result of medical enlargement of lymph nodes or other medical diseases.

As in the procedure of examination in other regions of the body, so it is in the cervical area that one pursues the classical method of inspection, palpation, auscultation and laboratory studies.

The procedure of inspection assists in localizing the lesion. Location is quite helpful in diagnosis because of the anatomy and embryology of the structures found in the neck. For example, a midline neck mass is usually thyroid in origin and rarely a dermoid cyst. A lateral mass anterior to the border of the sternomastoid muscle would indicate a branchial cyst or fistula. Inspection reveals the response of the tumor to motion. The thyroid masses move upward with deglutition as do masses of thyroglossal origin when the tongue is protruded.

Palpation assists in confirming the location of the mass. In addition, it gives valuable information as to size, shape and consistency, mobility and the presence or absence of pulsations. In the course of palpation the insertion of a finger into the depths of the oral cavity may reveal valuable information. This simple procedure differentiates neck masses from those arising from the floor of the mouth.

The use of the stethoscope is an aid in auscultation. The bruit over a vascular lesion, as in arteriovenous fistula or aneurysm, may be discerned via auscultation. A bruit is often heard over the thyroid gland in primary hyperthyroidism.

Roentgenograms are not taken often enough in the course of study for neck pathology. The x-ray should include study of the chest for many

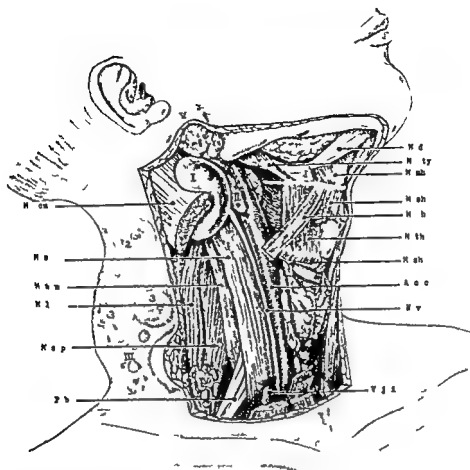


FIG. 5 Location of neck muscles in lateral and posterior aspect

Acp

A Metastatic thyroid cancer

I Fatty tumor *2* Sebaceous cyst *3* Infection carbuncle

I Branchial cyst *II* Carotid body tumor *III* Neurofibroma *IV* Hygroma *V*

Parotid tumor

M cm *M* sternocleidomastoid *M sa* *M* scalenus anterior *M sm* *M* scalenus medius *M ls* *M* levator scapulae *M ap* *M* scalenus posterior *P b* Plexus brachialis *M d* *M* digastricus *M sty* *M* stylohyoid *M mh* *M* mylohyoid *M sh* *M* sternohyoid *M oh* *M* omohyoid *M th* *M* thyrohyoid *A cc* *A* carotia communis *V c* *V* vena *V j i* *V* jugular interna

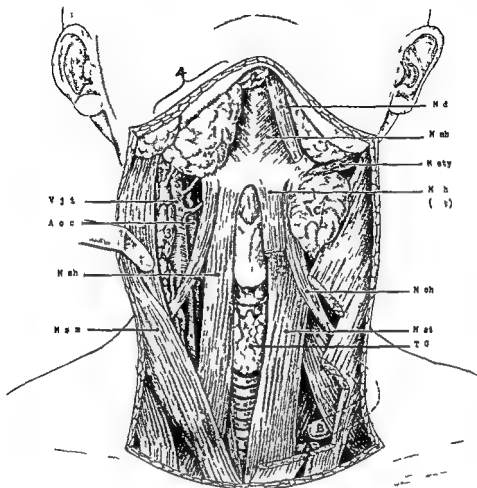


FIG 7 Location of masses in anterior aspect of neck

Key

A Virchow's node *B* Cervical rib *C* Teratoma

1 Enlarged sublingual gland due to obstruction of duct calculus or tumor *2* Sublingual gland enlargement *3* Lymphadenopathy *4* Mikulicz disease

Vji V jugularis interna *Aec* A. carotis communis *Msh* M. sternohyoideus *Msm* M. sternocleidomastoideus *Md* M. digastricus *Mmh* M. mylohyoideus *Msty* M. stylohyoideus *Moh* M. omohyoideus *Mat* M. sternothyroideus *TG* Thyroid gland

| | | |
|---|------------------|---|
| Rapid enlargement (after meals) | <u>indicate</u> | Esophageal
Diverticulum |
| Accelerated Progression (hours or days) | <u>indicates</u> | Acute
Inflammation
or hemorrhage |
| Slow development (weeks or months) | <u>indicate</u> | Chronic
Inflammation
(tuberculosis or
neoplasia) |

With a preliminary or tentative diagnosis available the examiner should then institute a mental differential diagnosis. By means of a simple classification many diseases can be eliminated and a more or more diseases in the neck identified (cf. Chart and Figures 7 and 8).

In general pathologic enlargements in the neck are due either to medical or surgical diseases. The medical diseases are inflammatory processes of the thyroid gland, lymphoma, and similar entities. Surgical lesions are those of thyroid origin, pathologic processes finding their origin in embryologic disturbances, or tumors either benign or malignant. By the process of elimination the diagnosis of tumor masses can be confined to a small number and then identified. The decision as to surgical intervention can be determined with adequate identification.

At this point one may well describe the characteristics of the thyroid gland on physical examination. The gland is hard (after iodination especially) and the superior poles come to a blunt point (similar to a tent). When nodules are present the gland may harbor cancer, multiple adenoma, or hyperparathyroid tumor. In order to palpate the gland adequately the examiner should stand in front of the patient and turn the patient's head toward the side to be examined. This will relax the sternocleidomastoid muscle. The examiner uses one hand to push the larynx toward the side to be examined. With the other hand the thumb is pressed anterior to the sternocleidomastoid muscle and the second and third fingers are placed posterior to this muscle. The patient is then instructed to swallow. In so doing the gland may be adequately palpated. In this way the length and breadth of the thyroid, the isthmus and the superior and inferior poles can be examined. Thus the shape, size, and consistency of the gland can be evaluated. When the lower pole is not felt a roentgenogram of the trachea is indicated in order to determine tracheal deviation, substernal and/or subclavicular extension.

The classification charts on pages 36 and 38, although not complete, will be an aid in differentiating the most commonly seen simple neck tumors.

Classification of Neoplasms of the Thyroid

| Me | L | S | MAN | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L | L |
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may be seen on the map on page 44 (Fig 13). The black area on this map are for the most part mountainous regions or old glacial areas. In terrain of this type most of the iodine has been washed out and carried via the rivers into the sea. A very low concentration of environmental iodine is characteristic of all these countries. Herein lies the cause of endemic goiter. Endemic goiter is the response on the part of the thyroid gland to the iodine deficiency. Therefore the prevention of endemic goiter

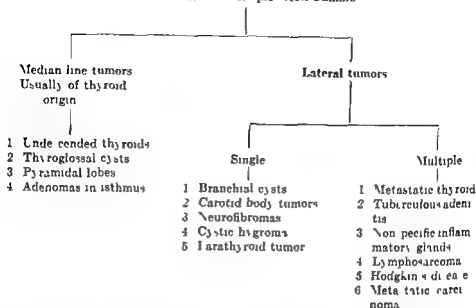


FIG 9 A method of examining the thyroid gland. The trachea and larynx are displaced toward the side to be examined. The index finger and the other fingers are placed behind the sternocleidomastoid muscle and the thumb is placed anterior to the muscle. The patient is then asked to swallow and in this fashion the thyroid gland can be palpated satisfactorily. Each lobe of the thyroid should be palpated separately. In addition to size, shape and consistency, each lobe is carefully examined for the presence of nodules. (Courtesy of the Mayo Clinic. Pemberton J. and Black B. M. Cancer of the Thyroid. Am. Cancer Soc. 1964.)

from a physiological point of view revolves about a substitution of artificial iodine for the natural iodine deficiency. Artificial iodination over a period of years will in the course of time insure a goiter free community. Those patients in whom endemic goiter has developed naturally will not respond to the administration of iodine. That is to say, iodine given to a patient with an existing endemic goiter will not dissolve that goiter. The only method whereby a pre existing visible goiter can be removed is by means of the surgeon's scalpel.

In the consideration of endemic goiter the most efficacious therapy is prophylaxis. Various methods of administering iodine as a goiter prophylaxis

Classification of Simple Neck Tumors



On occasion the surgeon may examine a patient with toxic thyroid symptoms and not find anything of significance in the gland itself. However he may palpate one two or more nodules along the anterior border of the sternocleidomastoid muscle. These nodules may be lymph nodes with metastatic thyroid tissue. At one time it was thought that these nodules were 'aberrant thyroid tissue'. More recent study indicates that these lesions are metastases arising from primary thyroid cancer.²¹⁻²⁶ When the examiner encounters a patient as mentioned above a study of the following table will enable him to differentiate metastatic thyroid nodules from other diseases producing nodules along the anterior border of the sternocleidomastoid muscle (Cf table 3 pages 40-41)

Endemic Goiter

Within recent years there has been accepted into the lexicon of medicine a new word called *geomedicine*. Geomedicine is the study of the natural history of disease by means of comparing the clinical picture of certain illnesses in one locality with the clinical picture of the same disease as revealed in another geographical location. A classical example of the value of geomedicine is masterfully exemplified in the book entitled 'Endemic Goiter' in which man's adaptation to iodine deficiency is studied.

Geomedicine has been of especial interest to the students of endemic goiter. There are various endemic goiter regions in the world. Their location

| Metastatic
thyroid
tumors | Usually under
40 | Single or multiple
masses occurring
in chains along
sternomastoid
muscle | Movable gland
like masses | May be none | 3 to 15 yr af-
ter onset of dis-
ease with
adequate
treatment | Capillary
ectasiaemia
or papillary
adenocarci-
noma |
|---------------------------------|---------------------|--|------------------------------|-------------|---|---|
|---------------------------------|---------------------|--|------------------------------|-------------|---|---|

* This chart is taken from Aberrant Thyroid by Frank H. Fisher and Bernard J. Lasser. Reproduced by permission of Surg-
Gynec & Obst 82: 70-11, 1946.

TABLE 3 Differential Diagnosis of Main Diseases Confused with Metastatic Tumors Arising in Thyroid Gland

| Disease | Age | Distribution of lesions | Characteristic features | Antecedent diseases | Course | Biopsy |
|----------------------|------------------------|--|---------------------------------------|---|--|---|
| Tuberculosis | Infants and children | Associated with general or local lymphadenopathy | Tender glands caseous matted together | Evidence of tuberculo elsewhere occasionally | Chronic | Lymph node containing Langhans giant cells tubercles |
| Lymphosarcoma | Usually over 40 | Main group of cervical glands involved | Large matted glands not tender | Debility picture of chronic illness | Usually fatal within 1 year | Lymph node with actively proliferating lymphoid cells in fine reticulum |
| Hodgkin's | Mainly young adults | Local glandular enlargement gradually becoming generalized | Massive discrete glands not tender | Fever (Pel-Ebstein type) eosinophilia | Chronic with fatal outcome in 2 to 4 years | Lymph node with Reed-Sternberg giant cells and eosinophils |
| Inflammatory glands | Any age | Regional glandular enlargement according to area infected | Enlarged tender glands | Evidence of primary infection fever leukocytosis | Rapid recovery with treatment | Hyperplasia of lymph node |
| Metastatic carcinoma | Usually elderly adults | Usually 1 or 2 prominent glands | Hard firm glands | Evidence of cancer in thyroid pharynx stomach or lung | Gradually downhill and fatal | Metastatic carcinoma |

has been tried. The most satisfactory method is iodized salt. The quantity of iodine necessary to add to table salt in order to prevent goiter is very minimal. To be exact, all that is needed is one part iodine to 100,000 parts of salt (1:100,000).

The anatomy of endemic goiter (adenomatous colloid goiter) is such that it is made chiefly of solid nodules and cysts. Both these cysts and nodules



FIG. 12. Photograph taken in the Peruvian Andes showing a large endemic goiter. This patient did not have respiratory distress and was not cyanotic. Since the thyroid is so close to the trachea one might expect some tracheal compression and respiratory embarrassment. This did not occur in this young man because the goiter is in a dependent position and external in front of the sternum. This position in fact pulls the goiter away from the trachea rather than pressing or occluding it. (Courtesy of E. A. Sharp and F. H. Payne of Parke Davis & Co., Detroit, Michigan.)



FIG 10 Anatomy of cervical lymphadenopathy (Reprinted from Pfizer *Spectrum* appearing in the J A M A)

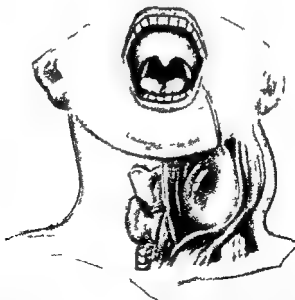


FIG 11 Anatomic location of branchiogenic cysts Cysts and fistulas of branchiogenic origin are usually found along the anterolateral side of the neck from the supra auricular region to the clavicle This is in contradistinction to cysts and fistulas of thyroglossal origin which are found in the midline (Reprinted from Pfizer *Spectrum* appearing in the J A M A)

vary in size from microscopic diameters up to tennis or golf ball size. The solid nodules will be similar to the common types of benign thyroid adenoma. It is rare to find malignant tissue in this type of goiter. The cysts themselves may contain material which in consistency may vary from thick jelly or cheese like material to clear fluid (degenerated cysts with inactivated colloid). Variation in the appearance of the cysts from pale water color to dark brown or black (old hemorrhage) may be noted. Some cysts are very thin walled and break during manipulation. Coarse trabeculation with thick fibrous tissue and scattered islands of parenchymatous tissue are seen under the microscope. In addition microscopic study demonstrates high columnar epithelium resembling the hyperplastic thyroid tissue of Graves' disease. This hyperplasia will be seen especially in the cysts in cases of adenomatous colloid goiter with secondary hyperthyroidism. The epithelial lining of the large follicles and the cysts is of the squamous type.

Calcium as a Goitrogenic Agent

In a geometrical study of the distribution of goiter, thought must necessarily be given to calcium as a factor in the causation of goiter. The calcium theory was put forth about one hundred years ago but was not subjected to much thought or consideration until more recent years when *geomedieine* commenced to demonstrate the importance of calcium. It appears that calcium may act as a goitrogenic agent although the precise conditions of diet under which it exercises its effect are not fully understood. It is known that iodine can counteract the goitrogenic action of calcium in some instances by preventing thyroid hyperplasia in others by establishing a colloid gland. A field survey covering an area of 1000 square miles performed in Calcutta, India, in 1835 led J. McClelland to report his findings to the Medical and Physical Society of Calcutta. He concluded that the cause of goiter in that locality was associated with limestone formations and was water borne. According to him, Goitre does not depend on temperature, altitude or aspect of irregularities on the surface of the earth, on hereditary taint nor on the usual causes of glandular enlargements in other parts of the body. McClelland probably was the first to systematically attempt to correlate the geological features with the occurrence of goiter. He brought attention to the fact that the damp calcareous *bhat* soil in the Gonda and Gandak valleys east of Gorakhpur are goitrous areas whereas the dry siliceous *bangar* soils in the Gogra valley to the south of same district are non goitrous.

In 1931 Baumann and his associates published in the *Journal of Biological Chemistry* results on thyroid deficiency caused by feeding rabbits with cabbage until a palpable goiter was produced. They showed that these animals retained calcium, magnesium and phosphorus. The ad-



FIG. 15 Microscopic picture of adenomatous colloid goiter. The well filled colloid vesicles of varying sizes and shapes are prominent (Price L. W. Histology of the Thyroid Gland. Medicine Illustrated Feb. 1949.)



FIG. 16 Microscopic section of colloid adenoma (or adenomata) as seen in colloid goiter. The presence of giant like colloid filled acini and the attenuated vesicular epithelium are characteristic of this entity (Price L. W. Histology of the Thyroid Gland. Medicine Illustrated Feb. 1949.)

ministration of a small amount of iodine converts such thyroid to the normal colloid containing state and restores the balance of these elements by increasing the amount excreted. The investigators believed that the retention of calcium is directly associated with the development of simple goiter.

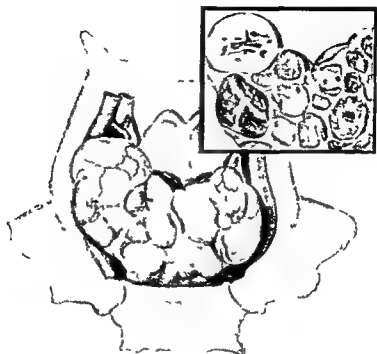


FIG 14 Anatomy of adenomatous colloid goiter also termed nontoxic nodular goiter. Insert shows a fetal adenoma. The structure of fetal adenoma presents the microscopic picture of numerous small alveoli lined by low cuboidal epithelium without colloid. Another type of fetal adenoma contains small round cells with heavily stained nuclei. In both types the periphery of the tumor is composed of closely packed cells. When these cells are densely packed the structure may resemble sarcoma. The embryonal character of the cells is noticeable hence the name fetal adenoma. Fetal adenoma is usually a benign lesion but it may give rise to adenocarcinoma, carcinoma and possibly sarcoma. (From Pfizer Spectrum appearing in the J. A. M. A.)

In 1934 Hellwig in the *Journal of Endocrinology* demonstrated that calcium chloride administered orally produced hyperplasia and thyroid enlargement in rats. He later demonstrated that thyroid adenomas were observed in white rats fed on a calcium rich goitrogenic diet. The nodules originate not from fetal rests but from differentiated thyroid epithelium. He believed they were due to the same stimulus which causes diffuse hyperplasia and represent an intermediate stage between hyper

Aureomycin and the Thyroid Gland

In the October 29 1954 *isue of Science* a report was published suggesting that there was a growth stimulating property of the antibiotics which was attributable to the antithyroid effect. This study failed to confirm any antithyroid effect of the antibiotic aureomycin. This study by Wil on C. Grant demonstrated that in no case did aureomycin produce significant change in the weight of the thyroid gland after forty days of feeding it to experimental animals.³³ His results differed from those of other (B. Calnick, W. D. Harris and R. S. Jones *Science* 119: 128, 1954) not only in degree but in direction. Grant concluded that aureomycin failed to produce a significant change in the thyroid gland as to size and actually caused a small but definite increase in the uptake of radioactive iodine.³⁴ The effect of antibiotics on the thyroid gland is being studied further.

Case Report: HYPERTHYROIDISM IN AN AMERICAN INDIAN (AN ANTHROPOLOGICAL NOTE)

Interest in thyroid disease never wanes. The clinical and pathological aspects of hyperthyroidism are enthusiastically studied by the surgeon and internist with equal satisfaction. Several years ago a hyperthyroid patient was treated without any apparent difference between him and many others seen previously. However during his postoperative stay in the hospital conversation with his immediate family brought to light that he was a full blooded American Indian. Never having encountered hyperthyroidism in an American Indian and not having read of a similar case in the current literature it was thought that this case presentation would interest students of thyroid disease. This clinical entity is infrequently seen in American Indians. For this reason the case is worthy of recording.

The degree of the Indian integration into our civilization affects the incidence of such ailments as hyperthyroidism and tuberculosis in this segment of our population the ailments becoming a rough measure of the integration and a matter of anthropological interest.

The patient M.S. a 55 year-old ironworker was seen for the first time in November 1941. At that time he was under treatment by his family physician for hyperthyroidism. He had the classical symptoms: nervousness, weight loss, palpitation, tremor, exophthalmos and signs of cardiac insufficiency. He was classified as a thyrocardiac. A H.M.R. taken was +35. He had never been ill until the onset of this illness which according to his history was of two months duration.

After an adequate preoperative regimen he was subjected to subtotal thyroidectomy. His postoperative course was uneventful and he was discharged from the hospital.

During the patient's postoperative period his immediate family was seen for the first time. Their general external appearance was similar to that of any other patient. However close observation revealed characteristics of the red race. This led to questioning and a subsequent lesson on American Indian.

The patient informed me that he was a full blooded American Indian of the Mohawk tribe. The Mohawks were members of the Iroquois League. The strongest

plasia and malignant tumor. He later demonstrated that the blood calcium in animals with parenchymatous goiters is double that of those with colloid goiters.

There is no doubt that there is an intimate relationship between the parathyroid gland and the metabolism of calcium. However, it is not common knowledge that the literature presents evidence to the effect that there is an intimate relationship between thyroid function and calcium metabolism. This can be demonstrated when one evaluates the marked



FIG 17 Photomicrograph of a thyroid adenoma demonstrating the separation of the acini by an increase in the supporting matrix due to gelatinous degeneration. This increase in supporting matrix and separation compression of the acini identify this lesion as a parenchymatous type of adenoma (Price L W. Histology of the Thyroid Gland. Medicine Illustrated. Feb. 1919).

changes which take place in the calcium balance of patients with thyroid disease. When thyroid activity is excessive as in thyrotoxicosis, calcium excretion is abnormally high. In patients having myxedema the opposite is true, namely that calcium is retained. As a general statement, the metabolism of phosphorus parallels that of the calcium. In 1942 J. D. Robertson suggested that thyroxine affected the renal threshold for calcium. The excessive secretion of thyroxine in thyrotoxicosis lowers the threshold whereas the deficient secretion in myxedema raises it. The corresponding elevated excretion of phosphorus in thyrotoxicosis and its lowered excretion in myxedema are secondary to the changes in calcium excretion. The proper administration of iodine in such patients reduces the high calcium output almost to normal and that of phosphorus to normal.

4

Hemorrhage and Pain in the Thyroid Gland

Thyroid Enlargement Due to Hemorrhage

MANY unusual occurrences are noted in the thyroid gland. Two of the more common are sudden thyroid enlargement and the presence of pain in the gland. An unusual cause for a sudden rapid enlargement of the thyroid gland is acute hemorrhage. This type of thyroid enlargement usually is confined to the older patient but may occur in any age group. Of the patients observed by the author five were over sixty years of age and three were in their twenties. All were women. In all but one of the six patients a preceding enlargement of the thyroid gland was present without toxic symptoms. However, a sudden massive enlargement of the gland prompted medical attention. The reason for the anxiety was difficulty in breathing and wheezing respirations. A detailed report of an unusual case is presented.

Case Report of sudden hemorrhage in a geriatric patient

A seventy-three year old housewife was interviewed for the first time in January, 1950. At that time she presented the history of an enlargement of the thyroid gland to massive size over a period of four months. She had a small mass in her neck for twenty-five years. The sudden growth of the mass in the neck was associated with respiratory distress and wheezing noises with expiration and inspiration. Respiratory relief was obtained when the patient lay up in bed which caused the mass to come forward and cease to compress the trachea.

In April, 1950 a total thyroidectomy was performed. Massive cystic adenomata were removed. Within the adenomata were found yellowish fluid and old blood clot. An elective tracheotomy was performed at the time of operation. The postoperative course was uneventful and the patient was discharged with complete freedom from her respiratory distress.

The operative specimen was carefully studied. The large areas of thyroid tissue were well circumscribed chronic adenomata with cystic degeneration. Yellowish fluid and old blood clots were contained within the cysts. Arterioles were found showing marked arteriosclerosis was also evident.

of all the Indian groups living east of the Mississippi River were the five tribes composing the Iroquoian League or Five Nations. These tribes—the Mohawk, Oneida, Onondagas, Cayugas and Seneca—held the land from Lake Huron to the Atlantic Coast and south through New York and Pennsylvania. Today the Iroquois live on reservations in New York State and Ontario. Their population is about 1,000.

The father of the patient under discussion lived on a New York reservation. The son left the reservation as a child and lived in the city. He settled in Brooklyn where there is a small colony of Indians. This colony is located in the less desirable part of Brooklyn. Most of the men in this colony earn their living as ironworkers.

Many of these Indians or their fathers before them adopted names of flower plants or trees. Others are called after parts of a tree as Branch, Leaf, etc. Our patient was named after a part of a plant.

Recently, according to a follow-up letter, it has been learned that this patient has developed pleural effusion (1964). The etiology probably is tuberculosis, which disease results in an extremely high mortality in the red race.

Addenda

In the management of hyperthyroidism the Italian school of therapy has utilized reserpine and analogous drugs. They have found that reserpine decreased the patient's anxiety, nervousness and insomnia. The drug was used in conjunction with any other medication prescribed in the treatment of the disease. They found no ill effects when reserpine was given in conjunction with the thiouracil compounds.⁶⁴

A recent survey in Tasmania has revealed a thyroid blocking agent as a cause of endemic goiter. It has been found that cows who have been fed one of the Brassicæ (chou moulter, thousand-headed kale) produce a milk containing an antithyroid substance namely, 1,5-vinyl-2-thiooxazolidone. This is an interesting revelation since endemic goiter was found in children and as we all know milk is an essential part of every child's diet.^{65,66}

4

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The operative specimen was carefully studied. The large areas of thyroid tissue were well circumscribed chronic adenomata with cystic degeneration. Yellow serous fluid and old blood clots were contained within the cysts. Arterioles were found showing marked arteriosclerosis as was also evident



FIG 18 Thyroid enlargement due to hemorrhage (lateral view)



FIG 18a Anterior view of the same patient as in figure 18

clinically by palpation of one of the major blood vessels. The entire pathologic picture was consistent with a rupture of an arterio-ecrotic blood vessel with hemorrhage into previous adenomata. The hemorrhage increased the size of the gland until the pressure within the gland equalized or became greater than the systemic blood pressure. When this stage was reached bleeding ceased. The result however was a marked enlargement of the thyroid gland with compression of adjacent structures.

Pain as a Symptom in Thyroid Disease

The presence of pain in thyroid disease is not mentioned frequently among its symptoms. When pain does occur in the gland it indicates one of two pathologic processes. The first is acute or subacute thyroiditis (strumitis or inflammatory goiter). The second is hemorrhage in the thyroid gland or in an adenoma.

Typical inflammatory processes in the thyroid gland are not as common as other thyroid diseases. For the purpose of this discussion our interest is focused on acute thyroiditis since it is this entity in which sudden pain occurs. Acute thyroiditis usually occurs as a complication of another infection. Pre-existing infections such as rheumatic fever, typhoid fever, measles, acute infections in the teeth, throat, upper respiratory tract or any generalized infection resulting in septicemia may antedate the onset of acute thyroiditis. When acute thyroiditis occurs, pain is a pronounced symptom and tenderness is elicited upon palpation of the gland.¹⁰³ (Other instances of thyroid pain will be discussed later.)

The occurrence of hemorrhage in thyroid disease usually occurs in an adenoma. Sudden rapid enlargement of an adenomatous goiter may indicate a rather large hemorrhage. This may occur in an elderly patient with arterio-sclerosis. The etiologic basis for this hemorrhage is rupture of an arterio-ecrotic vessel. This results in a cystic adenoma filled with blood. Pain occurs with the onset of the hemorrhage. Palpation of the gland elicits a painful response on the part of the patient.

Hemorrhage of small degree may occur in old adenomata of the thyroid. The hemorrhage results from capillary bleeding and stains the thyroid tissue a deep red or brown depending upon the duration of the hemorrhage. When an adenoma of this type is removed at operation and an immediate cross section was taken the hemorrhage can be seen upon gross examination. In the elderly patients the occurrence of pain is a prominent feature of the symptom complex. The pain continues even after the acute bleeding has ceased.

Toxic Adenoma (Plummer's Disease)

In toxic adenoma hemorrhage is less frequently seen than in non toxic adenoma. In toxic adenoma the tumor alone over-secretes and is therefore



FIG. 10 Roentgenogram showing a calcified adenoma of the thyroid removed from a 53 year old housewife with adenomatous goiter

hyperactive. The remainder of the thyroid tissue functions normally. In primary hyperthyroidism (Graves disease) the entire gland functions excessively. This fact has been studied and proven by giving patient tracer doses of radioactive iodine. It has been well established by animal experimentation that the uptake of labeled iodine by the thyroid gland is

a dependable index of the rate of secretory activity of the thyroid cell. Perhaps the fact that in non-toxic adenoma there is a freedom from excessive hyperactivity predisposes the non-toxic adenoma to hemorrhage. This may be based upon the fact that a toxic adenoma utilizes all available



FIG. 70. A 58-year-old housewife with typical features of apathetic hyperthyroidism. Note the wrinkled skin, weight loss, and the expression of apathy. Arrows point to thyroid enlargement. Note venous displacement to the left side. Basal metabolic rate was +100; pulse 160. Muscular fibrillation was present. Following thyroidectomy the patient had an uneventful recovery. The term "apathetic hyperthyroidism" has been used as a synonym for apathetic hyperthyroidism.

arterial blood to the area and hence there is no increment of blood available to result in a hemorrhage. Whatever the explanation may be, a serial study of many toxic and non-toxic adenomata discloses that hemorrhage in a solitary toxic adenoma is much less frequently seen than in non-toxic adenoma.

Chronic hemorrhage in the thyroid gland may be identified long after the hemorrhage has occurred. When an adenoma is sectioned and calcium

Toxic Adenoma (Plummer's Disease)

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FIG 19 Roentgenogram showing a calcified adenoma of the thyroid removed from a 53 year old housewife with adenomatous goiter

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5

Mental Symptoms in Hyperthyroidism

Psychosomatic Symptoms and Borderline Hyperthyroidism

THE SURGEON of yesterday little realized that posterity would demand a psychiatric knowledge in modern surgery. In the diagnosis and care of hyperthyroid patients the surgeon tre passes on the confines of the psychiatrist. Although he does not enter this domain, it cannot be denied that in the care of the borderline hyperthyroid patient the surgeon pierces the outskirts of this realm.

Psychosomatic medicine concerns itself with those patients who are neither physically ill nor have an organic mental derangement. The patients are categorized as having functional illnesses. Most of these individuals have a nervous disposition. A tremor may be present with palpitation occasionally noted. This triad of symptoms labels the patient a hyperthyroid. A basal metabolic rate is taken on the nervous patient. It is usually elevated. Failure to repeat this study does not reveal the error. The diagnosis is apparently correct and the patient is sent to the surgeon for thyroid surgery.

The surgeon now assumes the responsibility. Unless he is alert he will perform a thyroidectomy on a patient whose symptoms will persist or become more marked following surgical intervention.

Neurocirculatory asthenia, the most common disorder confused with hyperthyroidism. The individuals have palpitation, tachycardia, tremor, weight loss and a slightly elevated basal metabolism. Such patients however have no eye signs, no increase in pulse pressure or pulse rate. They do have a poor appetite, cold extremities and they demonstrate other manifestations of chronic anxiety.

Psychoneurotic states produced by psychic trauma simulate hyperthyroidism. A patient may have witnessed or been a party to a frightening experience. This factor may precipitate symptoms closely paralleling toxic goiter. This class of patient may have a pre-existing hyperadrenalism. The physical examination of such a person may not confirm the history.

is found, it may be postulated that a hemorrhage occurred months prior to the surgical identification of the calcified adenoma. Cystic degeneration in a diffuse adenomatous goiter may also contain calcium often in the shape, form and consistency of an eggshell. This finding indicates old hemorrhage in a cystic wall or in an adenoma which has undergone cystic degeneration.

Apathetic Hyperthyroidism

When a disease is not detected it cannot be treated. Apathetic hyperthyroidism is a type of hyperthyroidism which masquerades as heart disease. This term is used in contradistinction to the active hyperthyroid patient seen in adult life. The apathetic type of individual usually a female appears older than her years. The skin is wrinkled and evidence of weight loss is a prominent feature. There is no exophthalmos and no visible signs of excessive thyroid activity. The striking feature of this type of patient is the apathy revealed in the facial expression. Beneath this placid exterior, however, the heart rate is rapid and often irregular. The B.M.R. is often very high. As to the gland itself, it may or may not be enlarged. In those patients without thyroid enlargement an exact diagnosis may not be easy. Often these types of thyroid patients are not recognized as such. They are treated as cardiacs because of persistent tachycardia, arrhythmias or evidence of decompensation.

Although it is true that apathetic hyperthyroidism is not frequently seen nevertheless one should be aware of its existence. This type of patient responds well to proper thyroid surgery. Elimination of the cardiac complaints in the absence of decompensation almost always occurs. For this reason such patients as these should be properly identified and treated.

There are many other aspects of the thyroid symptom complex which will camouflage the underlying hyperthyroidism. The unusual feature of this fascinating disease will be discussed individually in succeeding chapters.

others. In such instance it is difficult to sift the mental class of symptoms from the hyperthyroid group. This type of patient however present many signs of hyperthyroidism which categorize the disease. Thus even if the mental complaints are attributed to hyperthyroidism at least the major underlying pathological condition has been identified.

Upon the thyroid surgeon rests the burden of separating borderline hyperthyroidism from functional disorders. His perspicuity and decision will save the neurotic from a needless thyroidectomy even as he escapes the trap of hypochondria from a patient with mild hyperthyroidism.

In a study of patients with hyperthyroidism attention was called to the close association between psychomatic symptoms and borderline hyperthyroidism. The fine differentiation between true hyperthyroidism and chronic fatigue or neurocirculatory phenomena has been treated. Additional observation of thyroid patients brought to light the frequency of mental symptoms in hyperthyroidism. The experience stimulated an interest in the unusual complaint manifested by patients with severe hyperthyroidism.

Phobia as a Symptom in Hyperthyroidism

During the past ten years (1947-1957) 356 primary hyperthyroid patients were carefully questioned as to the presence or absence of phobias.⁸³ No leading questions were asked the only suggestive questioning was

Are you very nervous? By careful interrogation the presence of a phobia was elicited without difficulty. The phobias were accordingly grouped as follows:

| Type of Phobia | N | % | F |
|--|-----|----|-----|
| Claustrophobia (fear of confined places) | 135 | 6 | 190 |
| Monophobia (fear of being alone) | 66 | — | 66 |
| Ochlophobia (fear of crowd) | 43 | 3 | 42 |
| Acrophobia (fear of high place) | 47 | — | 49 |
| Anthrophobia (fear of men) | 15 | — | 15 |
| Gynophobia (fear of women) | 29 | 22 | — |
| Hematophobia (fear of blood) | 6 | — | — |
| Nyctophobia (fear of the dark) | 6 | — | 6 |
| Zoophobia (fear of animals) | 12 | — | 12 |
| Taphophobia (fear of being buried alive) | 4 | 4 | — |
| Astraphobia (fear of thunder) | 3 | — | 3 |

From this survey it can be appreciated that phobia in excessive thyroid metabolism is not rare. It may easily be overlooked if the physician fails to recall that mental symptoms are often present in patients with hyperthyroidism.

of tremor, sweating and tachycardia. The gland may be normal to inspection and palpation without any audible bruit. The value of the pulse rate which is increased in hyperthyroidism is noteworthy. Psychic factors may cause a temporary elevation whereas hyperthyroidism maintains a constant elevation of the pulse rate. A fact to remember is that the toxic goiter patient is usually older than the neurotic individual. It has been observed that patients with true hyperthyroidism often have a tendency to cry spontaneously without apparent cause.

When the basal metabolism has been elevated on the initial reading technical inaccuracies may be the cause. The nervous individual should be informed of the procedure and his cooperation obtained. As a generality it may be stated that cooperation and relaxation are less frequently obtained with psychoneurotic patients than with hyperthyroid individuals. Repetition of the test each morning until a satisfactory technical reading is obtained may reward the observer with a normal basal metabolic recording. Radioactive iodine uptake is a very valuable diagnostic procedure in determining the presence of true hyperthyroidism.^{90, 91} (See other diagnostic aids.)

Another important differentiating observation is the apparent improvement when these functionally disturbed patients are hospitalized. When these persons are liberated from familial entanglements relief occurs within a few days. Freedom from noxious mental stimuli eradicates the tachycardia and nervous symptoms.

When persons with mental unrest have been convinced of the functional nature of their complaints and are assisted by competent helpful psychiatric suggestions improvement is noted. With the aid of a psychiatrist the so-called hyperthyroid patient undergoes a complete metamorphosis. All patients suspected of mild hyperthyroidism do not fall into the category stressed even as the diagnosis between a functional disorder and borderline hyperthyroidism is not as facile as outlined above. Each individual is a singular problem. There is no one diagnostic pattern applicable to all patients.

Caution is advised against the other extreme of failing to recognize a true borderline hyperthyroid patient. To brand such a patient a hypochondriac, a malingerer or a neurotic may produce deleterious results. It must also be realized that hyperthyroidism is a manifestation of a constitutional disease and as such may produce unusual psychic reactions. Although no characteristic psychic reaction is indigenous of hyperthyroidism many of these patients have acute delirium. Some patients with long-standing hyperthyroidism may manifest toxic exhaustion psychosis and others a chronic depressive reaction.

True mental disease may occur in the hyperthyroid individual as in

she commenced to dislike her self because the men trusted. Over a period of months she developed a hatred of men trusting as a womanly trait. Finally a homo sexual temperament and characteristics became manifest. Another female patient feared the sight of blood to an unprecedented degree. She refused to eat red meat because of the blood. Fainting at the sight of someone bleeding was a common experience with her. In spite of this she adapted her self well to her menstrual cycle. Following thyroidectomy and prolonged psychological therapy her hemophobia disappeared.

Hyperthyroidism and Neurosis

A purposeful study of the mental attitude of the hyperthyroid patient has revealed an interesting psychologic component in the individual. Two results of this study were previously discussed. One of them distinguished psychosomatic symptoms from borderline hyperthyroidism. The other unfolded major phobias in patients with primary hyperthyroidism.⁹⁰⁻⁹³ A continuation of this study concerned the presence of neurotic symptoms in hyperthyroid patients, the existence of hyperthyroidism in neurotic individuals, and the relationship between this mental state and organic thyroid disease. Prior to discussing the three categories of patients thought must be given to the present concept of neurosis and the abnormal influence of hyperthyroidism on somatic physiology.

A neurosis must be considered as a definite mental illness frequently encountered in modern medicine. Mental illnesses in general must be interpreted as the inability of the individual to mold himself into the environmental pattern. Some serious mental ailments have been labelled as psychoses, milder illnesses with a mental component have been called neuroses or psychoneuroses. In most cases of neurosis the person is made sensitive to or has been conditioned by inhibited childhood experiences. The disease becomes manifested by an acute emotional crisis. Anxiety is the root of psychoneurotic reactions. The patient is conscious of his anxiety state and is confronted by it with a demand for solution. He then attempts to follow some method leading to the solution of his problem. Inadequate handling of the situation results in conversion reaction or conversion hysteria. This conversion of anxiety into disordered functions of the organs or parts of the body is reflected in a train of symptoms which labels the patient a neurotic.

The neurotic symptomatology is limited. Symptoms are fundamentally characterized by intellectual and emotional reflections usually given the general label of nervousness. Complaints are identified by the title of nervous stomach, irritable heart, irritable colon, etc. Other symptoms reflect emotionalism in the guise of fears, doubts, anxieties, compulsions.

The above study indicates that the most frequently encountered fear is claustrophobia. The author remembered quite vividly a 26 year old white female with severe hyperthyroidism. She developed a Bell's palsy for which diathermy was advised. It was impossible to treat her because she could not tolerate the diathermy pads on her face. The pads gave her a sense of crowding and fear similar to being in a closed room. She was quite intelligent, a college graduate and volunteered the information that she had claustrophobia.

The second most common phobia in this series was the fear of being alone. Sixty six of the patients studied offered this complaint. One middle aged lady could not remain in her own home alone. When forced to do so she would telephone her friends and talk for hours in trivial conversation. Following thyroidectomy she became a taciturn matron.

The opposite situation was observed in 45 people. These individuals feared crowds and preferred to remain at home. This phobia often resulted in a pallid complexion because of the lack of sunshine. Most of these people would venture out of the house only in the darkness of evening.

Forty two patients had acrophobia. One patient, a 38 year old housewife, lived in an elegant 5 room sixth floor apartment overlooking the river. Her fear of high places was so severe that she would not look out the window although the view was most beautiful. She constantly quarrelled with her husband since she wanted to move out of the apartment. The scarcity of living accommodations was the source of the familial discord.

A fearful dislike of the opposite sex was unfolded in 37 cases. Fifteen women and twenty two men were so afflicted. A patient, recently seen in consultation with an internist, could not eat in the presence of a woman. He could not give the reason for his behavior but it was a constant experience. One day his buddy invited him to his home for dinner. He was assured that no women would be present. During the course of the dinner the friend's young married sister arrived unexpectedly. His appetite left him immediately. He could not take another mouthful of food. Following adequate thyroid surgery and psychiatric therapy, he married eventually becoming a proud father.

Other types of phobias in these patients were fear of blood, fear of the dark, thunder and fear of animals. A most interesting hyperthyroid person was a middle aged man who had taphephobia. His fear of being buried alive was so fixed in his mind that he left instructions in his will for an autopsy on his body. Another patient had violent fear of thunder. During a rain storm she would hide under her bed or run down the cellar to hide until the storm subsided.

Six patients exhibited intense fear of blood. All were young women, one of whom became frightened at her own menstrual flow. As time went on

inaccuracies are frequent. For the reason radioactive iodine uptake is a more valuable as it in diagnosis than the basal metabolic rate.

The patient with true hyperthyroidism is often overlooked because of the bizarre symptom occasionally encountered. In the usual hyperthyroidism no difficulty arises in making the diagnosis. It is the borderline patient who presents the difficulty and is often mishandled.

Case 1 An illustration of this type of patient concerns a 52 year old widow who had a thyroidectomy 5 years before her present complaint. The present illness of 6 months duration consisted of occasional trembling of arm and leg, intolerance to heat, frequent perspiration and emotional instability characterized by crying without apparent cause. She was sent to a psychiatrist who decided that she was neurotic as previously labeled by several physicians. At the time of her examination the significant findings were a rapid pulse of 120 B.M.R. +31 blood pressure 120/80. The left lobe of the thyroid was enlarged to 4 to 5 times. It could readily be seen and when called to the attention of the patient by a knowledge of seeing its existence shortly after her previous thyroidectomy. Her complaints were attributed to a psychiatric neurosis and she went from doctor to doctor until finally she was referred to a psychiatrist who believed he had organic disease. The diagnosis of hyperthyroidism was made and the patient was prepared for operation. At operation the left lobe of the thyroid was removed. Following surgery her condition markedly improved, she was free from her previous complaint and has now returned to the normal duties of a housewife.

Case 2 A 19 year old unmarried woman was treated for 8 years because of gastrointestinal symptoms characterized by nausea, sense of fullness and occasional diarrhea. In addition to this she was extremely nervous, very irritable and complained of arid palpitation. At the time of examination many of the above symptoms were confirmed also the fact that she had a phobia which was restricted in the form of crow is (ochlophobia). Her B.M.R. at this time was +25 pulse 106 and blood pressure 140/80. This patient was labeled a neurotic and was sent to a psychiatrist by an internist. It was only after the psychiatrist had a long talk with the individual that the diagnosis of hyperthyroidism was made. She was subsequently operated upon and at the time of this writing which is 5 years following operation she is a changed person without any of the previously mentioned complaints.

Men of medicine and surgeons who are conscious of the existence of thyroid disease often become overzealous in their diagnosis. The presence of nervousness, irritability and palpitation misleads the patient as having hyperthyroidism. This kind of symptoms may result in a thyroidectomy if the surgeon is not alert. Undoubtedly it has been the sad experience of many surgeons to have operated upon patients with true neurosis.

Case 3 A 25 year old woman employed by a telephone company was seen in consultation because of supposed hyperthyroidism. The patient was very nervous and irritable, had palpitation of the heart and a marked tremor. Her B.M.R. was +30. However after a series of readings it was found to be +5. Her pulse was normal, the blood pressure was normal. Thyroid was normal to palpation except for the isthmus which was slightly larger than normal. The clinical picture was not true hyperthyroidism. Finally consultation with a psychiatrist elicited the diagnosis of

and ob es ions An adequate history bring to light many hidden symptoms which formerly were simply called nervousne

Nervousne is a cardinal symptom in patients with toxic hyperthyroidism Excessive thyroid activity affects every organ of the body Hence tachycardia and gastrointestinal complaints are similar to those symptoms manifested by the neurotic individual To this symptomatology add phobia which has been considered as a new symptom in hyperthyroidism Fear being a common attribute of the neurotic patient the overlapping of symptomatology reflect the contiguous confusion in differentiating neurosis from hyperthyroidism



FIG 21 Normal thyroid showing microscopical view of follicles filled with colloid (Courtesy of Romaine Hieron Publishers Manhattan N Y)

Very often the surgeon must assume the responsibility of differentiating the true hyperthyroid patient from the neurotic one The psychoneurotic person may have witnessed or been a party to a frightening experience This factor may bring forward symptoms closely paralleling toxic goiter according to the mechanism previously mentioned The physical examination of such a person may not confirm the history of tremor sweating and tachycardia The gland may be normal to inspection and palpation without any audible bruit As mentioned previously the value of the pulse rate and pulse pressure is noteworthy Psychic factors cause a temporary elevation whereas hyperthyroidism maintains a constantly elevated pulse rate Emotionalism manifested by spontaneous tears without apparent cause is frequently elicited in true hyperthyroidism Elevated basal metabolic rate in neurotic patients may occur for several reasons since technical

on tries the presence of both neurosis and hyperthyroidism in the same patient. The case argue for perpicuity and care in diagnosing hyperthyroidism. They call to mind the pitfalls in labeling a person a neurotic without adequate study.

Modern surgery and psychiatry have become necessary supplements to the advancing knowledge of disease. In many cases the combination of thyroidectomy and intensive psychotherapy results in a disappearance of thyroid complaints and neurotic manifestation. The above case histories emphasize the need for an adequate case history, physical examination and laboratory studies in both neurotic and hyperthyroid patients. The dual cooperation between the surgeon and psychiatrist may save a neurotic patient from a needless thyroidectomy even as the surgeon's scalpel has eliminated prolonged psychological treatment of patients with hyperthyroidism.

Addenda

In recent months we have had available certain anti-neurotic drugs such as frenquel (azacvelonol hydrochloride) which have been used as therapeutic tests and as an aid in differentiating the neurotic from the hyperthyroid patient. Drug such as the e have had beneficial effects on neurotic patients who become emotionally stable under their influence.

anxiety neurosis. Thus it transpired that a patient referred by an internist for a thyroidectomy had in reality a neurosis.

It must not be forgotten, however, that true mental disease may occur in the hyperthyroid individual even as it may occur in any other person. When this situation exists it is difficult to sift the mental class of symptoms from the hyperthyroid group. Where a true mental disease exists in the hyperthyroid patient it is always found that there are many signs of hyperthyroidism which will categorize the disease. Thus even if the mental complaints are attributed to hyperthyroidism, the major underlying pathology will reveal itself by careful study.



FIG. 22 Primary hyperthyroidism (exophthalmic goiter) showing microscopic view of diffuse hyperplasia and papillary projections into acini indicative of accelerated glandular activity (Courtesy of Romaine Pierson Publishers, Manhasset, N. Y.)

Case 4. A 25-year-old unmarried woman presented the complaints of nervousness, palpitation and fear of crowds. This was of 6 months duration. Her pulse was 110, blood pressure was 140/70, B.M. III was +23. Examination of the thyroid revealed an enlarged right lobe and a slightly enlarged left lobe. The diagnosis was adenomatous goiter with secondary hyperthyroidism. In addition to this complaint the patient had typical symptoms of anxiety neurosis. She was seen in consultation with a psychiatrist who treated her for neurosis. Both the internist and the psychiatrist prepared her for operation.

When she had been successfully prepared thyroidectomy was performed followed by an eradication of thyroid symptoms. The psychiatrist then continued to treat her for neurosis. The thyroid symptoms disappeared soon after the operation but the neurotic symptoms manifested themselves as late as 4 months following surgery.

These cases illustrate several instances of problems in the differential diagnosis between neurosis and hyperthyroidism. The last example dem-

potassium thiocyanate in the treatment of arterial hypertension. There are many contraindications to and side effects of thiocyanate therapy. If the patient is not under constant observation the drug should not be administered. Specifically, blood thiocyanate determination is the only safe measure against serious toxic manifestations.

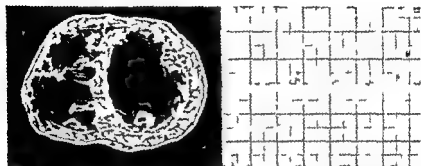


Fig. 77 Diagrammatic representation of a myxedema heart in cross section and the concomitant electrocardiograph finding. The anatomic section demonstrates general cardiac dilatation and enlargement of all the chambers of the heart. The inner white line represents the normal size of the heart. The electrocardiograph reveals flattened T waves. Cardiac impairment is the most frequent and prominent feature of myxedema (called myxedema heart by Zondek). A myxedema heart is characterized by generalized enlargement and dilatation of all four chambers. The muscular tonus of the heart is decreased, the pulse weakens and the circulation becomes slow. The blood pressure is not always low but may be maintained. The T waves in the electrocardiogram show changes which may be flattening or even inversion. Blood studies unfold a secondary anemia, high cholesterol and low levels of protein-bound iodine. (Courtesy of Warner-Chilcott Laboratories.)

Case report. The literature contains a report of acute gastric ulcer during thiocyanate therapy for hypertension.¹⁴ In this case the large gland atrophied and the associated hypothyroid phenomenon subsided under treatment with thyroid extract and iodides.

The patient reported here had a previous hemithyroidectomy performed for an adenoma in 1917. Exploration of the opposite lobe at the time of operation confirmed the absence of any left-sided adenoma. It is a well-known fact that a microscopic adenoma may have been unidentified at operation. Subsequent to her thyroidectomy the patient was given potassium thiocyanate and continued to take it without proper supervision. She developed a sensitivity to the drug which was controlled by an antihistamine preparation.

In November 1933 she manifested clinical symptoms of myxedema and a non-toxic adenoma was found on the side opposite to her previous hemithyroidectomy. It is believed that all of these manifestations, including the thyroid enlargement, are the results of the improper use of potassium thiocyanate.



FIG 25 Patient with myxedema (left) and the same patient after the administration of proloid for several weeks. The thyroid gland controls the body so effectively that its failure to function affects the entire organism even in an adult. In myxedema there is a generalized diminution in human function so that with severe myxedema the body is practically in a state of hibernation. The metabolic rate may fall to below 35, oxidation decreases and the metabolism of protein, minerals, carbohydrates and fats falls rapidly. Myxedema ascites may result with an associated retention of water, salt and protein in the intracellular fluids. (Courtesy of Warner Chilcott Laboratories.)



FIG 26 Hands of a female patient showing the changes resulting from myxedema. The skin is coarse, scale-like and thickened in appearance. The fingernails are retroverted. (Graham E. A. Surgical Diagnosis Philadelphia W. B. Saunders Co. 1930.)

With the objective in view the following is a general method of administering thyroid extract according to Means

| Age | Gr per Day |
|------------|-------------------------------|
| Up to 4 mo | $\frac{1}{10}$ |
| 4 to 8 mo | $\frac{1}{4}$ |
| 8 to 12 mo | $\frac{1}{2}$ |
| 1 to 2 yr | $\frac{1}{4}$ - $\frac{1}{2}$ |
| 2 to 4 yr | $\frac{1}{4}$ " |
| 4 to 12 yr | 1-4 |

In adult myxedema the underlying condition of the endocrine and physiological structure is not impaired and excellent effects from thyroid substitutive therapy are regularly obtained. Small doses must be employed at first and increased slowly at sufficiently long intervals until the symptoms are brought under control. Thereafter the patient will probably have to continue indefinitely on a maintenance dose of the hormone.

The thyroid requirement is usually found by beginning with doses of $\frac{1}{4}$ gr per day and after three weeks if no toxic manifestations have occurred doubling it. In this way the maintenance dose is found most often in the range of $\frac{1}{4}$ to 3 gr daily. Infants etc. are treated in the same way but their cerebral tolerance to thyroid extract is delicate and the effects of each increment in dosage must be observed carefully.

Means made a statement concerning myxedema (Cull & Clark) which is not worthy of repetition.¹¹⁰ He stated: "If one had been unable to arrive at a positive diagnosis in a myxedema like picture the presence or absence of characteristic response to thyroid would be of diagnostic significance. If while being treated for definite hypothyroidism with thyroid extract the patient went into Addisonian crisis the diagnosis of hypothyroidism due to primary hypopituitarism would be established."

Ascites in Myxedema

There have been only a few cases of ascites due to myxedema reported in the literature.³¹⁹ This complication may be a symptom of myxedema itself just as the periorbital or pretibial edema and pleural and pericardial effusions. It has been postulated that the cause for these changes is an alteration in the body proteins. However it must be remembered that ascites may be an expression of congestive heart failure due to myocardial degeneration secondary to myxedema or of coronary artery disease which has been found to be a frequent concomitant to myxedema. Differential

Mental Symptoms in Myxedema

In the neglected cases of myxedema (Gull's disease) a high incidence of psychosis is often manifested. As early as 1883, it was recognized that these mental symptoms were a definite clinical entity and contemporary psychiatrists would label this clinical picture as "myxedema madness". Some of these patients present a symptomatology of schizophrenia.² These unfortunate individuals may suffer from delusions, hallucinations, and mental deterioration. Even in the modern times it is not rare to encounter patients with a psychosis secondary to myxedema. Paranoid features are often manifested by many patients with advanced myxedema. Prior to the knowledge of the hormonal nature of their disturbances many of these patients were considered to be clinical examples of primary mental disease.

The increasing knowledge of the relationship between thyroid function and the brain is the basis for a new re-evaluation of the etiology of certain mental diseases. Many current authorities in the field of psychopathology have postulated that many psychoses may find their origin based on a neuroendocrine imbalance. Krapelin in 1917 wrote "cretinism is one of the few forms of insanity in which we can obtain at any rate an approximate idea of the connection between cause and effect".^{3,4} We have both in cretinism and myxedema examples of the fact that the destruction of a small constituent portion of the body may bring about severe disturbances in its whole economy and more especially may be the cause of insanity. Our knowledge of such relationships is of very recent origin. It is, therefore, conceivable that similar relations may some day be discovered in other forms of insanity.

When hypothyroidism is responsible for cerebral disfunction the administration of thyroid extract in small doses may have a dramatic beneficial effect. This is especially noted in the infantile or juvenile patients in whom there is the best chance for recovery under adequate treatment. McGavack has stated "Delays in beginning treatment affect the outlook for mental achievement more than the outcome for physical development".^{5,7} The effectiveness of thyroid extract is very well known. The only danger associated with the administration of thyroid extract is the possibility of overdosage. Means has found that a profound physiologic change can be produced in a patient by the administration of thyroid extract.¹⁰

^{3,10} This is especially true in children. In cretinism the amount of thyroid extract to be given depends upon the age of the patient. As a guide it may be stated that the amount of thyroid extract is such that will give the maximum therapeutic effects without even the slightest toxic manifestation.

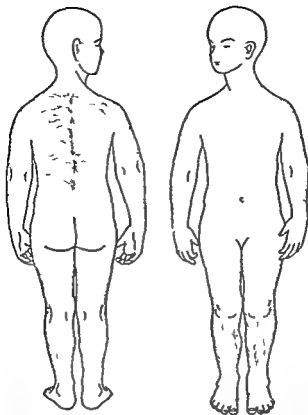


FIG 28 Drawing illustrating the distribution of hair in hypothyroid children. This unusual but typical hirsutism involving the back, shoulders, outer aspects of the arms and legs and to a lesser degree the sides of the face may be a manifestation of hypothyroidism in children (Larloff W H Hirsutism J A M A 157 No 8 1953)



FIG 29 Juvenile myxedema with goiter (Courtesy Warner Chilcott Laboratories)

diagnosis naturally is quite difficult. However, a study of the venous pressure and ascitic fluid high in protein and specific gravity would favor the belief that the ascites was a symptom of myxedema. Contrariwise, an elevated venous pressure and ascites with a low protein and specific gravity (transudate) would lead one to favor the presence of congestive heart failure. In either case the treatment must be outlined with great care. Small doses of thyroid extract are important for the management of primary myxedematous fluid accumulation. On the other hand digitalis, (its purified derivatives) diuretics and salt restriction are indicated in congestive heart failure.

Endemic and Sporadic Cretinism

Several centuries ago Felix Platter (Platerus 1536-1614), who occupied the chair of medicine at the University of Basle Switzerland, was one of the first men of medicine to give an accurate clinical description of cretinism and to note its relationship to endemic goiter.³⁰ He stated: "Wherefore the disease is frequent in certain regions in the beginning they write of it in Egypt and in Valesia Canton Bremis as indeed I have seen it myself and in the Carinthia valley called Bintzgerthal many infants are wont to be afflicted who besides their innate simple mindedness the head is now and then mis-formed the tongue immen-ent and flabby dumb, a struma often at the throat they show a deformed appearance and cated in solemn stateliness staring and a stick resting between their hands their bodies twisted variously, their eyes wide apart they show immoderate laughter and wonder at unknown things."³⁰

In certain areas of the world where simple goiter has been severely and continuously endemic over many generations the children of goiter bearing parents may be born with an almost complete lack of thyroid secretion. When this sad situation occurs in a child he is a goitrous degenerate and exhibits some of the typical physical and mental symptoms of hypothyroidism. This condition is known as endemic cretinism (in Europe referred to as cretine degeneration). It is most important to distinguish this from childhood myxedema (sporadic cretinism) with which it is often confused especially in infancy.

Endemic cretinism and sporadic cretinism (infantile or childhood myxedema) are two separate and distinct thyroid diseases unrelated except for the fact that they both involve hypothyroidism. They differ markedly in their etiology, pathology, symptomatology and in their response to proper treatment. Under the term endemic cretinism is classified all the cases resulting from over more than one generation of an insufficiency of iodine and in whom the thyroid gland is almost always enlarged. These

Hyperthyroidism, Puberty and the Reproductive Process

Physiological Enlargement of the Thyroid

AS AN EXPRESSION of the normal physiological development many young girls show evidence of a slight to moderate soft enlargement of the thyroid gland at or about the age of puberty. This enlargement which is an expression of normal thyroid activity is of short duration transitory in type and almost always leaves no residual thyroid damage. On rare occasions the thyroid enlargement however may persist after puberty and may be consistent with normal health and activity. Such enlargements of the thyroid gland are not pathological and cannot accurately be indicated as the precursors of thyroid disease which may occur in later life. An analogous alteration in the size of the thyroid gland is noted due to menstruation and pregnancy. During these physiological endocrine functions (menstrual cycle and pregnancy) an alteration in the size of the thyroid gland must be regarded as a normal accompaniment of sexual and reproductive activity. It is for this reason that the literature often refers to this type of thyroid enlargement as physiological adolescent school or puberty goiter. The alterations in the thyroid gland are so common during puberty that they are rarely noticed and often dismissed without comment in a discussion of thyroid disturbances.¹⁰³⁻¹¹

The onset of puberty in a girl like pregnancy and lactation places an added burden upon the thyroid gland. If during this period a young girl has a deficiency in dietary iodine the thyroid hormone may become temporarily disturbed due to iodine inadequacy. Thyroid enlargement may be the response to this physiological iodine inadequacy. However when the limited iodine intake no longer exists and a sufficient amount is available the thyroid enlargement may subside and the gland will assume its normal size shape and consistency. On the other hand if the iodine supply is really sufficient there is enough available to meet the demands of the body in all phases of its development. Therefore there will be no evidence of this so called physiological enlargement of the thyroid gland.

Succinctly therefore it may be stated that physiological enlargement

patients are always born of goitrous parents. Under the term childhood myxedema (sporadic cretinism) are categorized those patients in which the etiology is the same as in adult myxedema. This type of myxedema is not due to an iodine deficiency but to complete atrophy or congenital absence of the thyroid gland. Sporadic cretins are rarely born of goitrous parents and in view of the atrophy of the thyroid gland this condition must be considered as non goitrous.

Skin Test for Myxedema in Children

In certain problem patients when a diagnosis of myxedema is difficult or borderline a study of the skin may be revealing.

Biopsy specimens of dermal connective tissue may reveal alterations pathognomonic of hypothyroidism in children. Diagnostic histopathologic changes were observed in 15 of 26 patients with definite hypothyroidism and in 8 of 21 individuals with the suspected disease. No changes were observed in 52 euthyroid children reported Dr. Henning Andersen and associates of the Dronning Louises Børnehospital and the University Institute of Medical Anatomy, Copenhagen.^{5,6} Criteria of positive specimens include increased numbers and granulation of mast cells, edema, altered state of blood vessels and texture of fibrils and pronounced degrees of metachromasia and keratosis. Failure to observe metachromasia or other tissue changes in all myxedematous patients may be due to effects of previous thyroid therapy or to pituitary insufficiencies.

In some children the first sign of thyroid deficiency may be a hyperkeratosis of the elbows and knee manifested by stubbornly dirty patches for hypothyroidism assumes many forms.

To diagnose the condition correctly and as early as possible more than the classical tests are often employed. A simple and readily available diagnostic test for borderline hypothyroidism consists of administration of small doses of thyroid over a period of several weeks.



FIG. 30 Primary hyperthyroidism before puberty. Patient was a 10 year old girl with classic hyperthyroid symptomatology. BMR +70. Arrows indicate site of enlarged thyroid gland (Graham I. A. Surgical Diagnosis Philadelphia W. B. Saunders 1930)



FIG. 31 Nontoxic goiter before puberty. Insert is artist's drawing of microscopic section showing nontoxic goiter (From Fixer *Spectrum* appearing in the J. A. M. A.)

of the thyroid during puberty is a normal manifestation. When this type of physiological enlargement is seen it should not be dismissed as an inevitable accompaniment of puberty but thought must be given to the possibility of a borderline iodine deficiency which can easily be corrected by the administration of iodine orally.

It may be the erroneous belief of some that toxic goiter is a disease of adults. Although it is true that hyperthyroidism in children is not very common, nevertheless it does occur. Usually the initiating factor of hyperthyroidism is contained within the syndrome of primary hyperthyroidism and is often more acute than that observed in adults. The exact etiology of hyperthyroidism in children like that in adults, is not clearly understood. Predisposition may play an important part. Superimposed upon this congenital foundation an exciting cause may initiate the disease. Among these exciting causes attention is called to psychic trauma, over exercise, and focal or general infections. The incidence of hyperthyroidism in children is usually based upon the number of cases in proportion to the number of adults having the disease in a given series. In the literature written on this subject the ratio varies between 1 and 5 per cent.¹⁰³ Seventy per cent of all cases of hyperthyroidism in children occurs during puberty. When a child approaches puberty therefore many symptoms may be erroneously interpreted or discounted as insignificant. For this reason a resume of the salient features of hyperthyroidism before puberty is not unimportant.

Of the classical symptoms of hyperthyroidism the four most frequently seen in children are nervousness, tachycardia, exophthalmos and enlarged thyroid.

In considering nervousness a child may be observed to be restless in bed. This type of restlessness may or may not be associated with enuresis. Hyperactivity, restlessness and emotional instability are equivalent to nervousness. Falling out of bed, sighing and crying during sleep are other expressions of nervousness. The above mentioned nervous equivalents with or without nervousness and irritability may be the expression of an initiating phase of hyperthyroidism in children.

Tachycardia is a constant finding in hyperthyroid children. It is rarely a subjective symptom. The heart rate varies between 90 and 180 beats per minute. There is a constantly elevated pulse pressure. Exophthalmos is not a common sign. When it is present it is of slight to moderate degree. It is rarely as severe as that seen in adults with severe hyperthyroidism.

In almost all hyperthyroid children the thyroid gland although not greatly enlarged is visibly or palpably larger than normal. When an adenomatous goiter with secondary hyperthyroidism is the basic pathology, then the gland is readily palpable and visibly enlarged.

a complete study as to the possibility of hyperthyroidism. Overactivity, constant tachycardia with or without a failure to gain weight are symptoms demanding investigation of hyperthyroid function.

The differential diagnosis between mild rheumatic fever, mild chorea, and mild hyperthyroidism in children is most difficult. Laboratory studies are an aid but do not enable an exact diagnosis to be reached with ease.



FIG. 37 Cystic hygroma of the neck (congenital cystic lymphangioma) to be differentiated from congenital goiter. Hygroma develops soon after birth and becomes quite large. It arises from dilated lymph vessels rarely causes symptoms of tracheal compression but is often inflamed producing redness of the overlying skin. This cyst usually contains clear serous fluid. Branchial cysts contain crumbly mucous or sebaceous material.

A most reliable diagnostic test is the beneficial response to iodine therapy (see previous discussion on Physiological Enlargement of The Thyroid). In order to arrive at a diagnosis of hyperthyroidism one must eliminate paroxysmal tachycardia, anemia, anxiety, neurosis, malnutrition and intestinal parasites. Other conditions may simulate an enlargement of the thyroid gland, e.g., a cervical fat pad may give the false impression of thyroid enlargement. In thin children the normal thyroid because of deficiency of adipose tissue may become prominent and be mistaken for an enlarged thyroid gland. A congenital thyroglossal cyst may be misconstrued as an enlarged thyroid lobe. A cyst is usually smaller than the

There are certain symptoms found in hyperthyroid children which are found in adults. They however are somewhat altered in the younger group. For example tremor when present closely resembles the purposeless movements of chorea. Gastrointestinal symptoms, as nausea, vomiting, diarrhea and abdominal pain occur in about 20 per cent of children with hyperthyroidism. On occasion a child may be suspected of having an acute surgical condition within the abdomen when in reality the underlying pathology is hyperthyroidism.

Muscular weakness may occur as an initial hyperthyroid complaint. This is similar to that seen in adults with hyperthyroidism but to a lesser degree. Quadriceps femoris muscular weakness can be demonstrated by asking the child to step up on a chair or by keeping his leg extended while sitting in a chair.

Other symptoms seen in adults are absent in children. The most important of these symptoms hyperhidrosis is not prominent in childhood hyperthyroidism. Another group of symptoms are found only in children. For example growth disturbances may occur. Skeletal growth is more rapid than average in hyperthyroid children. Epiphyseal ages are accelerated, teeth develop prematurely and a demineralization of the body skeleton may be noted. In toxic female children ovarian function is suppressed and secondary sexual characteristics develop slowly. Menstruation is inhibited and often absent. In boys there is a retardation of sexual maturity.

An additional feature of hyperthyroidism before puberty is that many hyperthyroid children develop their symptoms after an infectious disease. The most common infectious diseases are measles and pertussis. Another aspect of the clinical picture of hyperthyroidism in children is the possibility of having a patient born a cretin with a goiter and remain a cretin until hyperthyroidism develops. Psychiatrists have emphasized the fact that behavior disorders in children may be an expression of disturbed thyroid function. The proper evaluation of and a satisfactory differential diagnosis of symptoms are most essential in arriving at the diagnosis of hyperthyroidism in children.

Diagnosis and Differential Diagnosis

The diagnostic tests for children are essentially the same as those for an adult. An exception is that radioactive iodine is rarely given to children for diagnostic purposes. The BMR however is always looked upon with suspicion and doubt because of inaccuracies both technical and otherwise. In typical cases of hyperthyroidism the diagnosis is not difficult. It is the early stages of hyperthyroidism that are overlooked. Any child with an enlarged thyroid with nervousness or irritability deserves

thyroid gland itself and is located above the thyroid area. There is little if any movement of the cyst with deglutition. Any movement when present is lateral rather than vertical as is usually seen in the thyroid gland.

Congenital pop eyes may erroneously suggest the exophthalmos of hyperthyroidism. The congenital deformity usually occurs in myopia in conjunction with a shallow orbit or an increased anteroposterior dimension of the eyeball. A consultation with an ophthalmologist is necessary in some cases to eliminate hyperthyroidism.

From this diagnostic review it can be appreciated that often it is not easy to arrive at a proper diagnosis of early hyperthyroidism before puberty.

Treatment

The introduction of the newer antithyroid drugs has resulted in a change in the management of hyperthyroidism in children. Medical management is often attempted prior to more radical therapy. In the initial stage of the disease complete physical and mental rest is necessary. All stimulants are avoided including nonalcoholic beverages which contain caffeine. In addition to the general measures propylthiouracil etc. is administered. The antithyroid drug are well tolerated by children. The usual precaution similar to the administration of the drug to adults are taken. The dose may vary between 100 and 200 mg. daily.

There is a great tendency to spontaneous remission of hyperthyroid symptoms in children; therefore the results of medical treatment should be guarded. Other objections to the use of the thiouracil drugs are the possible development of leukopenia, agranulocytosis and their potential carcinogenic action. The hyperplasia they produce in the thyroid gland approaches malignant changes in many patients.

The hope that the antithyroid drugs would be a substitute for thyroidectomy has not materialized. When surgical treatment is decided upon a preoperative administration of Lugol's solution 10 drop daily with or without the antithyroid drug is given. The Lugol's solution is usually given for 3 weeks prior to operation. The use of organidin in the same dose as Lugol's is equally as efficacious.

Although thyroidectomy does not correct the primary underlying cause of hyperthyroidism nevertheless it has been the accepted therapy for decades. There is disagreement as to the amount of thyroid to be removed in a child as well as to the frequency of persistent hyperthyroidism and myxedema following operation. It is believed by many that the same amount of tissue should be removed as in an adult thyroidectomy. Recurrence of myxedema is not an uncommon postoperative experience. There is no indication that the preservation of more or less of the gland



FIG 334 A 2 month old male infant with congenital pop-eyes
B Closer view of infant showing that the proptosis is more marked on the left side
C Lateral view of the same infant with congenital proptosis

for one year prior to delivery. Hydramnios developed and the woman went into labor, delivering a girl of 34 weeks gestation weighing 4 lb 11/oz (1,843 Gm). The baby was born with a diffusely enlarged thyroid that was firm and nodular. The thyroid was so large that the head was held in retraction. When the infant began to have difficulty in swallowing 2 drops of Lugol's iodine solution were given daily. Episodes of cyanosis and difficulty in breathing necessitated frequent suction and oxygen. The thyroid enlargement subsided and the head retraction position gradually disappeared with the diminution in the size of the thyroid gland. The infant received desiccated thyroid substance 5 days after birth. The administration of this extract was stopped when the thyroid enlargement disappeared on the 36th day. Several days later a slight exophthalmos appeared. A few weeks later, when the baby was treated with sulfadiazine and sulfasuxidine because of diarrhea and cellulitis, the thyroid again became diffusely enlarged and severe head retraction recurred. When the administration of the sulfonamide preparations was discontinued the head retraction vanished along with the thyroid enlargement.

Although most mothers treated with thiouracil give birth to normal infants, about 20 to 30 per cent apparently show some effect on the fetal and neonatal human thyroid as a result of this drug. Furthermore, it has been reported that, in mothers receiving iodine with the antithyroid drugs, no abnormalities occurred in the offspring. This case report by Perlman negates this observation. In fact, goiter is known to occur in infants whose mothers have received iodine alone. It is felt that the antithyroid drugs should be discontinued during the last month of pregnancy. Thought should be given to the fact that during pregnancy the basal metabolism is normally elevated. The administration of thiouracil preparations therefore in sufficient amounts to produce a lowering of the basal metabolic rate in a nonpregnant woman would *de facto* produce a degree of hypothyroidism during pregnancy. The fear of producing hypothyroidism may be abolished if the antithyroid drugs are given for a short period of time only. In this case report it is conceivable that the recurrence of the goiter in this infant at the age of 2 months might well have been due to the sulfonamides. However, the rapid regression of the thyroid enlargement forces one to assume that this is purely speculative.¹

Pregnancy

From January 1, 1947 to December 31, 1957, in a series of over 650 patients operated upon for thyroid disease, only seven pregnant women with hyperthyroidism were encountered. Five of these patients had primary hyperthyroidism and the other 2 had adenomatous goiter with secondary

would give more satisfactory results. A point to mention is that there is a great tendency toward keloid formation in children following thyroidectomy.

In children psychotherapy may be as essential a regimen as it is for adults. While confined to bed the child has games, toys and books which amuse him and keep him happy. When the child becomes ambulatory and returns home excitement and crying may become a problem. The cooperation of a child psychiatrist is often as important postoperatively as the preoperative preparation for thyroidectomy.

An interesting account on juvenile thyrotoxicosis was reported in the *Journal of Pediatrics* in 1954. Allen and his associates reported the therapeutic results obtained from 30 children in whom symptoms of thyrotoxicosis appeared before the age of 15. Fifteen patients received thyroid irradiation with or without stable iodine, and 15 others received prolonged treatment with the antithyroid compounds. In this latter group some received iodine and others did not receive it. These authors did not employ radioactive iodine in children with thyrotoxicosis, because they do not believe that the possibility of late untoward sequelae can be excluded in this form of therapy. ⁴ The final therapeutic results could be fairly well evaluated in 24 of the 30 children under treatment. A satisfactory remission of the toxic thyroid symptoms was obtained in 17 of the 24 children. The results were similar in those who were irradiated and in those who received the antithyroid compounds. Five out of 6 children who were operated upon had a satisfactory remission of the disease following thyroidectomy. Allen and his associates feel however that thyrotoxic children without nodular goiters should be given a long trial with antithyroid medication before thyroidectomy is performed. They believe this in spite of the fact that the over-all results from nonsurgical therapy do not compare as favorably as those results known to follow thyroidectomy. The preservation of an anatomically intact thyroid gland for the proper adjustment of the endocrine stresses of puberty and the remaining growth period plus the low incidence of post therapeutic myxedema are the major considerations which prompt them to pursue a conservative therapeutic regimen. ⁴

Parman of Canada presented an interesting situation in which a goiter developed in a premature infant. ¹⁷⁵ The 26 year old mother of the infant whose case was presented by him had been taking 150 to 200 mg. of propylthiouracil daily for one year. The dosage of this drug was increased on occasion to twice the amount for 3 or 4 days at a time. The month before delivery the patient increased the dosage of propylthiouracil to 300 mg. per day. At the same time she was taking Lugol's iodine solution in amounts varying between 8 to 12 drops per day. The iodine was taken

Management of Hyperthyroidism during Pregnancy

Pregnancy leads to exacerbations of hyperthyroidism, so that the diagnosis is readily discerned. The major problem is of what therapy should be followed. It is medical treatment preferable to surgical intervention? It is necessary to know what is the opportunity for a thyroidectomy?

In the light of our present discussion it appears that the preferred use of the antithyroid drugs is not the method of choice. These drugs should not be used indiscriminately in the adenomatous type of gland with second



FIG. III Patient with moderately severe exophthalmic goiter (primary hyperthyroidism). Photograph illustrates markedly enlarged right and left lobes of thyroid gland. The thyroid isthmus is prominently visible.

ary hyperthyroidism. If necessary these drugs may be used in addition to Lugol's iodine as a preoperative regimen similar to the procedures followed in nonpregnant hyperthyroid patients. Thyroidectomy performed during the first half of pregnancy is the therapy of choice. Pregnant women tolerate thyroid operations very well and there is no indication for interrupting the pregnancy.

Summary of Hyperthyroidism and Pregnancy

1. Pregnant women may develop hyperthyroidism or pregnancy may cause an overt manifestation of latent hyperthyroidism or an exacerbation of true hyperthyroidism during a period of recrudescence.

hyperthyroidism All 7 patients displayed marked toxic symptoms. They were prepared for surgery and had an uneventful recovery.

These patients were seen by more than one physician, obstetrician and surgeon. Surgery was advocated by some and advised against by others. This was a source of great confusion to the patients. In view of this confusion, it is appropriate at this point to reiterate certain facts in reference to the problem of hyperthyroidism and pregnancy.

As a preliminary statement it must be recalled that a moderate hypertrophy of the thyroid gland occurs as a normal physiologic response to pregnancy. This hypertrophy occurs (especially during the last trimester of pregnancy) in 65 to 90 per cent of women who become pregnant. With or without thyroid hypertrophy there is a definite elevation in the B M P. This rise is approximately +5. The elevation in B M R is more pronounced during the last half of pregnancy. *Radioactive iodine should not be administered to a pregnant woman.*

In view of our present knowledge of the effects of hyperthyroidism on the liver it is worthy to recall that during pregnancy the liver is in a state of imbalance. If hyperthyroid stress is placed upon this disturbed equilibrium it is understandable that such a patient might easily develop the complications of pregnancy associated with liver pathology. Specific reference is made to eclampsia, vomiting of pregnancy and acute yellow atrophy of the liver. This fact is an argument in favor of the urgency of proper treatment of hyperthyroidism in pregnant women.

Other contributions to our knowledge of the thyroid gland in pregnancy were made by Halsted and Ukita.¹¹⁰ The former demonstrated that partial thyroidectomy in pregnant dogs resulted in a marked hypertrophy of the gland in the offspring in order to compensate for the deficient maternal secretion. Ukita showed that the removal of the thyroid gland from pregnant rabbits prolonged labor and the baby rabbits were undersized, poorly developed and their thyroid glands were hypertrophied with evidence of increased secretory activity. The glands of the non-pregnant animal were normal. It has been proven that the enlargement of the thyroid gland seen in pregnancy is due to a true hyperplasia of the acinar structures and to the formation of new follicles. In view of this hyperplasia it would be inadvisable to treat hyperthyroidism during pregnancy for a long period of time with antithyroid drugs because of the possibility of instituting carcinomatous changes. In addition the prolonged use of an antithyroid drug may result in a goiter in the offspring. If this does not occur the gland of the offspring is merely enlarged following the conventional use of the antithyroid drugs.

felt that the interrelationship of these disturbances cannot be explained fully at this time.

A comparative study made by Paxton and Herrmann on 2 groups of euthyroid patients complaining of sterility and menstrual disorders revealed the following. In an initial group of 339 patients only 131 could be considered for study. These 131 patients were divided into Group A (75 patients) and Group B (56 patients).¹⁴ The patients in Group A were treated empirically with thyroid extract. Group B received only placebo tablets. The thyroid activity of all patients was studied at regular intervals by means of the basal metabolic rate, protein bound iodine, radioactive iodine uptake and serum cholesterol determinations. It appeared to these investigators during this course of study that a single determination of any one of these laboratory tests especially the basal metabolic rate is not enough to evaluate thyroid function. Moreover it is frequently misleading especially in the euthyroid patient.

The information gathered revealed that the cure and improvement rates between Group A and Group B was not of much significance. It was the impression of Buxton and Herrmann that the exogenous thyroid administered to their patients merely replaced the endogenous thyroxine that the thyroid gland would ordinarily produce were it not permitted to rest (or hibernate as it were) because of the outstanding resistance in maintaining its function. Although this study by no means provides the final answer as to the efficacy of thyroid therapy in menstrual disturbances and sterility, the failure to find any statistically significant difference in the results obtained in the two groups studied clearly indicates that the therapeutic value of thyroid administration for sterility and menstrual abnormalities is very questionable.¹

The Thyroid and Reproductive Function

Associated with the discussion on the relationship between the thyroid gland and the reproductive function Herring stated his opinion that the minor degrees of hypothyroidism may be practically symptomless and yet may seriously affect reproductive processes (J.A.M.A. 113: 1300, 1939).

This conclusion was reached following the study of 150 patients. The discussion concerned itself with the causation of abortion and sterility in women. This report showed that in an unselected group of 150 pregnant women the greatest number of abortions occurred in those whose thyroid activity was below the normal standard. Inaccuracies might have occurred in this study since they based their diagnosis of hypothyroidism solely on the basal metabolic rate. In 61 of the 150 patients studied

2 Under any circumstance the hyperthyroidism and not the pregnancy should be interrupted

3 Failure to interrupt the thyrotoxicosis may result in a spontaneous interruption of the pregnancy by nature herself

4 Hyperthyroidism in pregnant women is treated satisfactorily by surgery, after adequate preoperative preparation, without the fear of losing the fetus

5 When thyroidectomy is performed during the first half of pregnancy the patient usually goes on to a full term normal delivery

6 Prolonged treatment of a pregnant woman with an antithyroid drug may produce a goiter in the infant or stimulate carcinomatous changes in the gland of the mother

7 Whenever possible it is advisable to inform patients that pregnancy should not be undertaken for at least one year, and preferably two years after thyroidectomy

8 Radioactive iodine is contraindicated during pregnancy

Effect of Thyroid Therapy on Menstruation and Sterility

It is well to recall some current thoughts on the effects of the administration of thyroid extract on certain problems peculiar to women. Thyroid therapy in the euthyroid obstetric and gynecologic patient has been open to much controversy during the past many years. It is a common clinical impression of gynecologists that thyroid extract is of great value in the treatment of sterility and menstrual disturbance. A contrary opinion is advanced by many internists, endocrinologists and thyroid specialists who offer much doubt concerning the efficacy of thyroid therapy for these conditions. Buxton and Herrmann have studied this problem quite intensively.¹³⁷

These authors reviewed the literature and found that thyroid extract was administered for a multivarious group of gynecological disorder. These disorders ranged from essential uterine hemorrhage, amenorrhea and oligomenorrhea to sterility and menstrual disorders. Actually there is no exact clear understanding of the relationship of the thyroid gland to the complicated mechanism of the pituitary-gonadal-endometrial axis. As a matter of fact Buxton and Herrmann have shown that the evidence advanced in the literature is in truth contradictory. Clinically speaking hypothyroidism as well as hyperthyroidism may be associated with every degree of menstrual disturbance from amenorrhea to acute metrorrhagia. These menstrual symptoms may be due to anovulation and other ovarian underfunctions occurring in thyroid disorders. It must be candidly con-

Thyroid Disease and the Climacterium

THE FINAL responsibility as to whether an operation is to be performed resides with the surgeon. It is his decision whether a thyroidectomy should be undertaken for the treatment of hyperthyroidism. The surgeon must know his patient thoroughly in order to treat hyperthyroidism. He cannot become a mere technician and leave the important field of diagnosis to other sources. Only in the proper knowledge of the patient's clinical background may he result in a needleless operation. In other situations thyroidectomy may eradicate mental symptoms and rehabilitate a person destined for a mental institution.

When a symptom complex is common to several clinical entities the possibility of confusion and error in diagnosis is understandable. Primary hyperthyroidism as a discrete entity may present initial symptoms easily confused with other illnesses. This is especially true when psychomotor irritability is reflected in emotional complexes and sympathetic hyperactivity.

In middle life when physiologic dysfunction results from a diminution in activity of the glands supplying male or female hormones many symptoms are produced. The menopausal symptoms result from an imbalance of equilibrium between the sympathetic and parasympathetic nervous system. When this imbalance is associated with disturbances in the psychic brain centers clinical manifestations result which closely simulate primary hyperthyroidism. If in addition to the climacteric symptom the patient happens to have a small or moderate sized thyroid gland an erroneous diagnosis of primary hyperthyroidism is easily made.

The frequency of symptoms elicited in hyperthyroidism and in the male and female menopause can be appreciated from a perusal of the accompanying table. Emotionalism, nervous irritability and excitability are symptoms of major importance in both climacteric and hyperthyroid patients. Often this grouping of complaints initiates the symptoms which bring the patient to seek medical attention. Not to arrive at a proper diagnosis at this time may result in improper management and therapeutic failure.

The sensation of warmth, hot flushes, intolerance to heat and free

hypothyroidism was demonstrated. In this group there was a total of 21 miscarriages either in previous pregnancies or in the pregnancy during which these observations were made. In contrast to this, the total number of all miscarriages in the normal and hyperthyroid groups together was only 9. From these results Herring concludes that the hypothyroid state is an important factor in the causation of fetal death and subsequent abortion and that this significance has not hitherto been sufficiently stressed.

From the foregoing study of common symptoms it can be appreciated that confusion rather than a mistake will result from a history alone. In the middle aged and menopausal group of patients the presenting symptoms closely parallel those noted in hyperthyroid individuals. Careful differential diagnosis, therefore, is especially important in this menopausal group.

The basal metabolic rate is not the *sine qua non* of diagnosis because many of the symptoms previously discussed would themselves produce an erroneous recording. When the basal metabolism has been elevated on the initial reading technical inaccuracies may be the cause. Repetition of the test each morning preceded by a mild dose of a barbiturate will reward the observer with a normal reading.

When doubt as to the true underlying disease cannot be honestly eradicated therapeutic tests are indicated. If border line hyperthyroidism cannot be eliminated Lugol's iodine may be administered. Improvement under this medication will indicate hyperthyroidism. Radioactive iodine is a valuable diagnostic aid as well. Similarly when the symptomatology favors a diagnosis of the menopausal syndrome hormones may be administered. Alleviation of the patient's symptoms during the administration of estrogens or testosterone will establish the climacteric diagnosis.

Equally worthy of study is the activity of the thyroid gland in the menopausal patient. Usually cessation of ovarian hormonal activity does not directly alter thyroid function. However a reflex effect on the thyroid gland through the pituitary gland may or may not occur. The master role of the pituitary on both ovarian and thyroid secretions is well known. Based upon this relationship thyroid hypofunction is allied to ovarian hypofunction during the climacterium. Clinically this has been observed in some women during the menopause. Often the robust woman at the time of her menopause will display certain features of thyroid insufficiency. She will gain weight but does not become obese. Her activities are diminished and are reflected in slowness of thought and action. Inability to keep awake, muscle fatigue and backache are frequent complaints. Other symptoms may be paresthesias of the hands, alopecia and dryness of the skin and hair.

This group of patients should be given thyroid extract in addition to the hormonal medications. Prior to administering thyroid extract a basal metabolic rate should be determined. The proper thyroid dosage is different for each patient. A satisfactory basal metabolic level is in the vicinity of -5 to -8 per cent. A suggested rapid method of raising the metabolic rate is to give 4 gr. of thyroid extract for 4 days then reducing the amount to a maintenance dosage of $1\frac{1}{2}$ gr. The basal metabolic rate should be checked once or twice weekly. When the basal metabolic level

perspiration are symptoms noted in both groups of patient. Careful interrogation will readily separate this group of complaints into their proper category. Hot flushes and the sensation of warmth are usually more marked during the menopause. Intolerance to heat and facile perspiration are more pronounced in hyperthyroidism. However, each of these symptoms is found in both hyperthyroidism and the climacterium.



FIG. 35 Primary hyperthyroidism with severe exophthalmos. Acute exacerbation occurred during menopause. This patient demonstrated the following eye signs: widening of palpebral fissure (Dalrymple-Stellwag's sign); failure of upper lid to follow eyeball in its downward movement (Von Graefe's sign); weakness of convergence of both eyes (Moebius sign); and in addition absence of normal wrinkling of forehead (Crossley's sign). (Graham E. A., *Surgical Diagnosis*, Philadelphia: W. B. Saunders Co., 1930.)

Mental symptoms have been noted in both types of patient. The symptoms may find expression as phobias and in advanced cases as true psychoses. A series of hyperthyroid patients studied for the presence of a phobia was previously discussed.⁹² This study revealed many phobias of different types. In menopausal patients the most frequent phobias are the fear of impending danger, the fear of crowds and the fear of inadequacy. This last fear finds its basis in the alteration of a previous full sex life. Adequate questioning and physical examination will aid greatly in placing the patient in the hyperthyroid or climacteric group.¹⁰¹

TABLE 4 *Group of Symptoms Common in Hyperthyroidism and the Climacterium*

| Symptom | Hyperthyroidism | Female Climacterium | Male Climacterium |
|------------------------|-----------------|---------------------|-------------------|
| Nervousness | + | + | + |
| Menstrual disturbances | + | + | |
| Disturbed sleep | +— | + | + |
| Irritability | + | + | + |
| Excitability | + | + | + |
| Hot flashes | + | + | + |
| (cessation of warmth) | | ++ | + |
| Intolerance to heat | + | + | + |
| Palpitation | + | + | + |
| Emotionalism (crying) | + | + | + |
| Free perspiration | + | + | + |
| Psychoses | + | + | + |

Thyroid Surgery in the Elderly

The usual clinical features of thyroid disease may be absent in the elderly patient. Even in aged persons with hyperthyroidism the effects of excessive thyroid activity are less pronounced than in the younger adult. Although fortunately hyperthyroidism is infrequent among the elderly, thyroid surgery has a place in the treatment of the aged patient.

Indications for surgical treatment are

- 1 Apathetic hyperthyroidism
- 2 Thyrocardiac disease
- 3 Tracheal compression secondary to adenomatous goiter
- 4 Cancer in the thyroid gland

1 Excessive hyperthyroidism in the aged may present itself as apathetic hyperthyroidism. This term describes the elderly patient with toxic hyperthyroidism who does not have exophthalmos, tremor and the other signs of hyperthyroidism. On the contrary, they have an indifferent or apathetic facies which beguiles the true underlying disease. These patients do have tachycardia and cardiac arrhythmias. Many of these individuals' signs are unrecognized and are treated as heart cases.

2 Hyperthyroid heart disease or thyrocardiac disease in the aged is seen by the surgeon as often as the internist. Apathetic hyperthyroidism is seen rarely by both surgeon and internist. Internists are alert to the presence of this etiological type of heart disease and make the correct diagnosis in almost all instances. The patient in spite of his age is rapidly prepared for surgery and with adequate surgery, excellent beneficial effects on the patient result. The internist is often able to control this type of cardiac patient with great ease following thyroidectomy.

is then established, the maintenance dose may be modified if it becomes necessary to do so. It may take one month to establish a maintenance dose by this method. Thyroid extract may be given for a period of 4 to 6 months.

The preferable method is to raise the metabolic rate slowly. Small doses of thyroid extract ($\frac{1}{2}$ gr. to 1 gr.) may be administered for 1 or 2 weeks. Following an interval of 2 to 3 weeks the dosage may be further increased. Associated with an elevation in the basal metabolic rate the patient becomes subjectively improved. The patient can be maintained with 1 or 2 grains of desiccated thyroid daily for 4 to 6 months.

Menopause and Hyperthyroidism

During the menopause the truism that 'once a hyperthyroid always a hyperthyroid' is recalled. The close harmonious linkage between the pituitary gland as the master regulator, the thyroid and the ovaries is distorted during the menopause. This discord results in many symptoms often difficult to separate into their proper clinical category. Frequently the menopause is associated with an acute exacerbation of thyroid symptoms in a patient who has had a thyroidectomy for hyperthyroidism. These patients should be given iodine during the period of treatment for menopausal complaints. Another type of patient develops hypothyroidism with the onset of the menopause. The rational administration of thyroid extract alleviates the hypothyroid picture. These facts stress the physiologic role of the thyroid gland during the climacterium. For this reason during the menopause special observation and consideration should be given to the post thyroidectomy patient as well as to other individuals with a previous thyroid history. The reason for this consideration is the fact that many menopausal symptoms can be attributed to thyroid activity.

Treatment of the thyroid dysfunction will alleviate many of the complaints attributed to the climacterium. This is especially true in those individuals who are not responsive to a prescribed rational therapeutic regimen for the control of the menopausal syndrome. These individuals may have an underlying thyroid state which when treated in conjunction with hormonal therapy will produce remarkable clinical improvement.

Often the similarity of complaints in the hyperthyroid and menopausal patient camouflages the underlying disease. This may result in erroneous treatment. Responsibility rests upon the surgeon. He must separate the climacteric individual from the true hyperthyroid patient. His watchfulness and final decision will prevent a thyroidectomy on a menopausal patient, even as he can erase many symptoms previously mentioned from those with true hyperthyroidism.

9

Thyroiditis

Struma Lymphomatosa

DISORDERS of the thyroid gland have fascinated surgeons since 1878 when Theodor Kocher first published his report of a successful thyroidectomy.¹ Accentuated interest in this subject found an impetus in 1912 when Hashimoto described a new pathologic entity in the thyroid gland. Since he was the first to describe the lesion it bears his name as well as the descriptive term struma lymphomatosa or lymphoid goiter.²

This clinicopathologic entity is unusual because of its low incidence as well as its bizarre pathologic picture and symptom complex. A study of the literature will show many discrepancies as to the exact number of cases reported since it was first described by Hashimoto. In order to clarify this problem A. C. Graham in 1931 studied the literature extensively.³ He divided the reported cases into ten categories interpreting and grouping them for statistical purposes. His analysis clearly demonstrated the existing confusion, duplication and lack of proper identification in the various cases reported. For this reason no accurate determination of the number of cases of struma lymphomatosa is possible. However up to the present time various authors have reported small series of cases. Thus it can be appreciated that this entity is infrequently encountered during the professional career of the average surgeon.

Etiology and Pathology

The exact causative factor in the production of struma lymphomatosa is unknown. It has been suggested that exhaustive atrophy is a recognized change in Hashimoto's struma and that this degeneration might be associated with some form of compensatory hyperplasia resulting in this disease. Graham's study has led him to express the opinion that there is no proof that hyperthyroidism, hypothyroidism, suppuration, tuberculosis, syphilis or neoplasia are factors in the causation of struma lymphomatosa. Although the exact nature of the condition has not been determined the current belief is that Hashimoto's disease should be included in the same category with Riedel's struma. Although frequently confused with Riedel's struma many authors have concurred in the opinion that Riedel's struma and Hashimoto's disease are two distinct pathologic entities.

■ An indication for surgical intervention in the aged thyroid patient is tracheal compression secondary to adenomatous goiter. Situations of this type were seen in ten elderly patients, all over 65, who presented a similar history of having a pre-existing goiter which suddenly increased in size. Associated with the sudden enlargement was 'wheezing' respiration and respiratory distress when lying flat in bed. The sudden thyroid enlargement is attributed to hemorrhage in a cystic adenoma. The hemorrhage arises from a rupture of an arteriosclerotic vessel in the adenomatous structure.

4 Elderly thyroid patients may be subjected to thyroid surgery for another reason, namely, carcinoma. In years gone by, the outlook for a patient with thyroid cancer was disheartening. Modern surgery, radioactive iodine and radiation therapy bring new hope to such victims. Elderly patients with advanced cancer are no longer given passive nursing care. Active treatment is now available, and when employed to its utmost can prolong the life of those who are advancing in years.

In the management of thyroid cancer the surgeon can perform an almost total thyroidectomy. This thyroidectomy may or may not be associated with a radical neck dissection on one or both sides of the neck. Following surgery, radiation therapy with or without the administration of radioactive iodine is a valuable supplement to the surgical procedure. Combined treatment of this kind has benefited many patients afflicted with thyroid cancer.

enclosed in the connective tissue. It is areas of this type which often lead to the erroneous belief that Hashimoto's disease is an early stage of Riedel's struma. Microscopic study of the blood vessels reveals no remarkable alteration in their normal architecture except for the fact that an abundance of round cell infiltration is noted around the larger vessels.

Thus struma lymphomatosa is a lymphoid goiter characterized by a growth of lymphatic element in the formation of lymphoid follicles together with certain changes both in the parenchyma and in the interstitial tissue of the thyroid gland.

TABLE 5 *Differentiation of Hashimoto's Disease and Riedel's Struma*

| Hashimoto's Disease | Riedel's Struma |
|--|--|
| It is practically always confined to women | Disease is reported equally in men and women |
| A history of myxedema may be obtained | There is little tendency toward myxedema especially following an operation |
| Glandular involvement is diffuse and bilateral | Involvement is usually unilateral following a discrete nodule |
| Pressure symptoms are of the tracheal constricting variety | Pressure symptoms such as hoarseness and difficulty in swallowing and limitation of the cord on the involved side are common |
| Inter glandular adhesions are absent | Pronounced adhesions to adjacent structures are found |
| Pyramidal lobe is prominent | Pyramidal lobe is usually not prominent |
| Histologically fibrosis is circumscribed | Histologically fibrosis is diffuse |
| Lymphoid hyperplasia is pronounced | There is no lymphoid hyperplasia |
| There are large lymph follicles present | Giant cells can be identified in the fibrous tissue |

Clinical Picture

The disease almost always occurs in women. It has an insidious onset and follows a chronic course. The duration of symptoms may vary from 9 months to 5 years or more. The clinical manifestations result from pressure of the hardened gland on the trachea. Usually there are no recent symptoms of a disturbed thyroid function in patients having the disease for a long period. When the disease is of a chronic nature, however, there is almost always an associated hypothyroidism at one time or another in the patient's past history. The basal metabolic rate is usually within normal limits. On occasion the basal metabolism may be below normal. Infrequently evidence of mild myxedema may be noted.

A classic clinical history of struma lymphomatosa may be given as follows. The patient is a 40 year old woman who for many years has had en-

Micropathologic study of this disease reveals a dense diffuse lymphoid infiltration between the follicles with occasional formation of secondary nodules. Sometimes the follicles are extremely prominent, so that the microscopic picture may closely simulate a lymph node. Hence the terminology struma lymphomatosa or, as it is sometimes called, lymphomatoid or lymphoid goiter. There tends to be a variation in the intensity of the lymphocytic infiltration from occasional scattered lymphocytes among colloid containing follicles or even absence of infiltration in certain

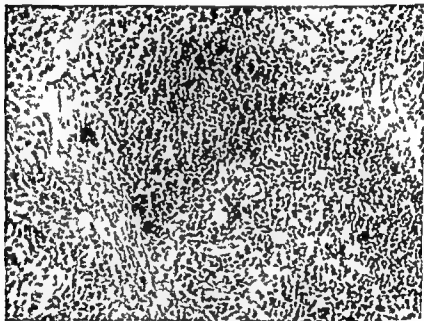


FIG. 36. Photomicrograph (170 \times) of histologic section of struma lymphomatosa. This low power view shows typical lymphocytic infiltration of the thyroid gland with a tendency toward formation of a structure simulating a lymph node.

areas, to complete displacement of the normal thyroid with confluent masses of lymphocytes forming secondary nodules. Other types of cells found are monocytes and occasionally plasmocytes. Notwithstanding the abundance of lymphocytic infiltration the lymphoid tissue does not demonstrate a definite formation of lymph node. That is, there is no formation of sinuses.

The connective tissue is usually swollen, poorly stained, and the cells have few nuclei. Mononuclear lymphocytes may be readily identified in the connective tissue. In rare instances the interlobular and intralobular connective tissue may be sufficiently increased to predominate over the lymphocytic infiltration. When this occurs small islands of follicles are

produces a soft gland and does not possess the physical characteristics of struma lymphomatosa. Calcified adenoma, either solitary or multiple, are readily identified by calcific roentgenographic evidence of this type of degeneration.

Struma lymphomatosa on occasion may be difficult to differentiate from neoplastic lesions. However it may be distinguished from malignant disease by the following points:

- 1 In struma lymphomatosa all areas of the gland are involved without serious encroachment on tissue outside the thyroid gland.
- 2 Neoplasia involves all areas including the main vessels and nerves.
- 3 Struma lymphomatosa does not produce an irregular nodular surface of the gland.
- 4 Regional glandular enlargement due to metastases is absent in struma lymphomatosa and is usually prominent in neoplasms.

Whenever a satisfactory differentiation between carcinoma of the thyroid and struma lymphomatosa is not possible pathologic study of the operative specimen will decide the question.

The present tendency among pathologists and surgeons is to regard struma lymphomatosa and Riedel's struma as distinct diseases. Often these entities are difficult to differentiate from each other. For this reason the foregoing table is significantly valuable. In addition to the points given Riedel's struma may be frozen in the neck. It is the hardest pathologic entity (except a calcified adenoma) felt in the neck. It is as hard as cartilage and cuts with difficulty. Hence it has been called variously iron struma, lignous or woody thyroiditis.

Treatment

Operation in struma lymphomatosa is indicated for two reasons: 1 to differentiate the lesion from cancer; 2 to relieve or prevent pressure symptoms. At the time of operation the true identity of the pathologic change in the thyroid is revealed. The gland with Hashimoto's disease is enlarged from 2 to 5 times the normal size. It is not adherent to adjacent structures. Thus it is immediately differentiated from cancer or Riedel's struma. The gland is gray pink in color and firm in consistency. When sectioned it is white with a suggestion of focal edema. Compression of the gland with a clamp results in the extrusion of a serous fluid. Clamps grasp the tissue poorly and hold fast only to the fibrous capsule and blood vessels in the gland parenchyma. Bleeding is not remarkable because of compression and at times complete occlusion of blood vessels. This occlusion results from an increased fibrofollicular pressure which is characteristic of Hashimoto's disease.

The surgical procedure is a routine subtotal thyroidectomy. However,

largement of the thyroid, which grew rather slowly. She complains of weakness, fatigability, slight nervousness and some pressure symptoms. The pressure symptoms may be described as hoarseness, choking or dysphagia. On occasion a brassy cough or a roughening of the voice may be noted.

The gland with Hashimoto's disease will unfold the following diagnostic criteria:

- 1 The gland has a diffuse pebbly feel
- 2 It feels as hard as exophthalmic goiter with iodine involution
- 3 The superior poles are extremely broad, being broader than the poles of primary hyperthyroidism
- 4 The pyramidal lobe is enlarged similar to the enlargement of the lobe in primary hyperthyroidism

By seeking to determine the presence of these criteria, one can make the preoperative diagnosis of struma lymphomatosa with accuracy in most instances.

Diagnosis

The most valuable clinical aids in arriving at a diagnosis of struma lymphomatosa are obtaining an adequate history and performing a satisfactory examination of the thyroid gland. If the signs and symptoms parallel the clinical picture previously presented, a tentative diagnosis of struma lymphomatosa can be made.

Struma lymphomatosa must be especially differentiated from other chronic infections and neoplasms of the thyroid gland. The most confusing lesions are:

- 1 Chronic nonspecific thyroiditis
- 2 Chronic specific thyroiditis
 - a Tuberculosis
 - b Syphilis
 - c Actinomycosis
- 3 Calcified adenomatous goiter
- 4 Lympho sarcoma
- 5 Carcinoma
- 6 Riedel's struma
- 7 De Quervain's disease

Non specific thyroiditis is eliminated immediately in arriving at a diagnosis since Hashimoto's disease displays the absence of acute inflammatory symptoms. Hashimoto's disease is bilateral, may be associated with hypothyroidism, and does not have a tendency toward spontaneous cure. Specific granulomatous lesions are differentiated by the absence of any specific evidence of the causative organisms of tuberculosis, syphilis or actinomycosis. The enlargement of the thyroid gland in specific infections usually

produces a soft gland and does not possess the physical characteristics of struma lymphomatosa. Calcified adenomas, either solitary or multiple, are readily identified by calcific roentgenographic evidence of the type of degeneration.

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the operation is less radical than that for primary hyperthyroidism. The remnants of the thyroid are sutured to the trachea in such a way that the midline of the trachea is free of thyroid tissue. By the prevention of continuity of the remnants of the thyroid the possibility of future tracheal compression is avoided.

Recurrent compression of the trachea may result following thyroidectomy. This recurrence is occasioned by a contraction of scar tissue which



FIG. 37 Microscopic section illustrating an important point in the histologic differentiation of Riedel's struma from Hashimoto's struma. In Riedel's struma there is a persistence of normal colloid in some acini as shown here. The fibroblastic reaction which precedes and accompanies the fibrotic process may be confused with spindle cell sarcoma. (Price I. W. Histology of the thyroid gland. Medicine Illustrated Feb. 1919.)

has replaced the removed thyroid glandular elements. When this situation occurs the tracheal compression may be sufficient enough to diminish the size of the trachea. With this diminution in size there may be an interference with the respiratory quotient of the lungs. A second surgical procedure is rarely necessary for thyroiditis. Occasionally, when severe tracheal constriction results from excessive scar tissue formation, surgical correction may become necessary. When this situation is encountered further constriction can be avoided by suturing the prethyroid muscle to the trachea over any remaining thyroid tissue on either side of the trachea. This will prevent, in most cases, the formation of any scar tissue from developing between the musculotracheal suture site in the future.



FIG 38 Gross specimen of the thyroid gland (cross section of a lobe) showing the dense white appearance of Riedel's struma with central liquefaction and cyst formation (Price L W Histology of the thyroid gland Medicine Illustrated Feb 1949)



FIG 39 Riedel's struma showing dense fibrosis of the capsule with extension into adjacent muscle tissue (Barr D P Thyroiditis and myxedema Bull New York Acad Med July 1953)

The postoperative course is usually uncomplicated. Brawny thickening of the cutaneous layers may occur, and may persist for many weeks. In most instances myxedema can be anticipated. Patients should be advised of this possibility prior to operation. Patients are followed postoperatively with routine determinations of the basal metabolic rate, the cholesterol level, and protein bound iodine for this reason. Control of the myxedema is not difficult with a daily dose of thyroid extract. After operation, these patients are much relieved and are considered well as soon as the myxedema is controlled. There have been no reported instances of recurrence of the disease following thyroidectomy. Operative mortality does not differ from the mortality in routine subtotal thyroidectomies.

Prognosis

Untreated struma lymphomatosa may pass into myxedema. After thyroidectomy, complete and permanent relief of pressure symptoms results although the onset of hypothyroidism may be accelerated. If this condition is anticipated, the postoperative administration of thyroid extract should be commenced as soon as incipient myxedema is suspected.

Postoperative recurrence is unusual. So called recurrence can be attributed to inadequate surgical treatment. This occurs if the bilateral nature of the disease is not recognized and results in a unilateral resection which fails to adequately relieve the pressure symptoms. It is a mistake to assume that the disease has in the interval merely spread from one lateral lobe to the other for which view there is no reliable evidence. The explanation is most probably that in certain asymmetrical goiters (based on congenital asymmetry of the thyroid gland) one large lateral lobe may so overshadow the other small lobe that the latter is allowed to remain undisturbed." 9

Résumé on Hashimoto's Disease

Many studies have indicated that Hashimoto's disease is listed among the rarer surgical entities. The salient feature of this disease is that its exact causation is unknown. It occurs almost entirely in women in the third, fourth and fifth decades of life. The fundamental pathologic change is a lymphocytic infiltration associated with follicular pressure atrophy. Vascular channels are obstructed because of fibrofollicular pressure. Clinically, the most important findings are demonstrated by palpation of the thyroid gland. The features of struma lymphomatosa are broadening and enlargement of the superior poles and hard firm lobes giving the impression of a pebbly surface. Enlargement of the pyramidal lobe as in hyperthyroidism is notable. Pressure symptoms may or may not be present.

Surgical treatment is indicated to relieve pressure symptoms and to differentiate the disease from neoplasm

Little is known at present as to the course of untreated Hashimoto's disease since patients in all the reported cases have been subjected to operation or radiation therapy. Thyroidectomy will relieve pressure and nervous symptoms. If postoperative myxedema occurs, it can be counteracted by the administration of thyroid extract

De Quervain's Disease

Any discussion on thyroiditis would be deficient without some mention of De Quervain's disease. Clinically De Quervain's thyroiditis does not imitate Riedel's struma. It may, however, occasionally resemble Hashimoto's disease when fever, pain and thyroid tenderness are present in struma lymphomatosa.

The composite clinical picture of De Quervain's disease is as follows:

- 1 It is most common in women (of any age)
- 2 It has an acute febrile onset
- 3 Fever, leukocytosis and a rapid sedimentation rate are common
- 4 The thyroid gland is tender to palpation
- 5 Pain in the gland is referred to the ears and mandible
- 6 The thyroid gland may enlarge bilaterally to twice its normal size
- 7 The duration of the disease is from several days to several weeks
- 8 It is a self-limited disease with recovery the usual end result
- 9 A small uptake of radioactive iodine is usual with a greater than normal urinary excretion of I^{131}

It is interesting to note that the response of De Quervain's disease to radioactive iodine is similar to that observed in advanced myxedematous although the patients exhibit none of the clinical manifestations of hypothyroidism.^{1, 5, 10} Contrariwise during the active stages some symptoms and signs suggest thyrotoxicosis.^{11, 12, 13} Hence radioactive iodine is of value in the differential diagnosis between primary hyperthyroidism and De Quervain's disease.

The pathologic changes in De Quervain's disease are quite different from Riedel's struma and Hashimoto's disease. Pathologic material for study of this interesting inflammatory thyroid lesion has not been frequently available and is not easily obtained. Thirty-two years elapsed between De Quervain's first and second publications.^{10, 11} During these years he was able to examine only a few new cases and from the reports of others he could identify only 62 cases.

Pathologically in the early active stages of the disease large areas of the thyroid gland show a destructive process. The acinar cells of the thy-

roid follicles disappear and their former location is recognizable only by the persistence of residual colloid after partial spillage into the surrounding tissue spaces. Around the former acini there are numerous extremely large



FIG. 40 De Quervain's thyroiditis, exhibiting extensive destruction of thyroid acini and numerous multinucleated giant cells (Barr D P. Thyroiditis and myxedema. Bull. New York Acad. Med. July 1953.)

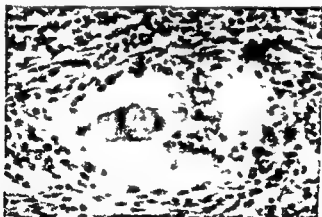


FIG. 41 High power view of De Quervain's thyroiditis showing the relation of the multinuclear cells to the surrounding tissue (Barr D P. Thyroiditis and myxedema. Bull. New York Acad. Med. July 1953.)

multinuclear cells. These apparently have phagocytized the colloid and constitute the most distinctive and diagnostic feature of the disease.

During the acute phase there may be considerable infiltration with lymphocytes plasma cells and polymorphonuclear leukocytes. Small abscesses have been observed at different stages of the disease. As the disease

progress is marked fibrous tissue reaction occurs which is so marked that De Quervain's disease may be reported by the pathologist as Riedel's struma.



FIG. 4 Photomicrograph of an operative thyroid specimen removed from a 39 year old housewife whose major complaint was tracheal constriction. At the time of operation the gross appearance of the gland suggested struma lymphomatosa. The histologic picture is that of De Quervain's disease. It is interesting to note that the pathologist described this section originally as Riedel's struma and later altered his opinion in favor of De Quervain's disease.

The Reticuloses

Certain diseases of other endocrine glands besides the lymphoid system, may alter the architecture of the thyroid gland. This is especially noted in Mikulicz's disease which involves the salivary and lacrimal glands. The lymphoid hyperplasia that occurs in the submandibular and lacrimal glands may appear in the thyroid gland as well. Thus it must be remembered that a patient with Mikulicz's disease may have an associated lymphoid hyperplasia of the thyroid gland.

When sarcoidosis is generalized a hypertrophy of the thyroid gland may occur. Microscopic examination demonstrates a diffuse lymphoid infiltration in the thyroid gland. Clinically, the thyroid gland may or may not be enlarged.

Sjogren's disease is similar to lymphoid hyperplasia of the thyroid gland.

The presence of this disease may alter the histological picture of the thyroid gland in some individuals. The same statement may be made in reference to lymphosarcoma. Apropos of this statement Levitt writes "I studied a patient who displayed the clinical characteristics of so called Hashimoto's disease. She eventually died and the autopsy revealed lymphosarcoma. Lymphosarcoma could be differentiated from early fibrolymphoid hyperplasia of Hashimoto by the relative absence of extrathyroid involvement in the latter. In the earlier stages of lymphosarcoma, however the thyroid does not manifest characteristic surface changes or fixation. The rapidly lethal course of lymphosarcoma soon proves the diagnosis."¹⁴

Treatment of Nonsuppurative Thyroiditis

The increasing frequency of acute thyroiditis subsequent to upper respiratory infections and as a manifestation of systemic infection, has enabled the clinician to arrive at an efficacious method of therapy. In the past many drugs have been employed to counteract thyroiditis. Among these were the sulfonamides, the antithyroid drugs and more recently the antibiotics. It has been found that the best mode of therapy for acute thyroiditis of nonspecific and nonsuppurative type is to administer the steroids. A regimen of exceptional value is to give the patient 80 mg. of ACTH intramuscularly for 3 days. Following the parenteral route, cortisone is prescribed for oral administration. It is given in 25 mg. tablets every 6 hours for 2 days, then every 8 hours for the third and fourth days and finally every 12 hours for the final 2 days. After this course of therapy the thyroid gland returns to normal. An indication that the inflammation has disappeared is the absence of pain on palpation and the disappearance of any glandular enlargement. The use of ACTH and cortisone as just outlined is as of now the most satisfactory method of treating nonsuppurative acute or subacute thyroiditis.

Hurthle Cell Adenoma of the Thyroid

The Hurthle cell tumor is among the surgical pathologic entities encountered in thyroid surgery and one of the rarer adenomata seen in the thyroid gland.

Hurthle in 1894, described a large oxyphilic para-follicular thyroid cell as part of the normal thyroid gland.³⁹⁷ Lymphans described the same cell in tumors of the thyroid. Later these cells were found in association with adenomas and adenocarcinomas of the thyroid and have since been known as Hurthle cell tumors. The origin of the Hurthle cell tumor has not been defined explicitly.³⁴⁹ Wilensky and Kaufman have discussed in detail the histogenesis of the Hurthle cell. Suffice it to say that the Hurthle cell ha

been traced to several different origins by various writers. Erienberg and Wallerstein believed that the tumors were of parathyroid origin³⁴⁹. Gettowa claimed that the Hurthle cell came from ultimobranchial bodies³⁵⁴. Others as pointed out by Wilensky and Kaufman, believed that the

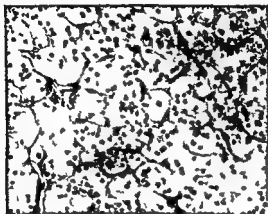


FIG 43 Low power histologic section showing Hurthle cell adenoma of the thyroid gland. The characteristic histologic features are trabeculae and the large vacuolated cells.



FIG 44 Microscopic section showing carcinoma which has developed in a Hurthle cell adenoma. This section resembles the benign adenoma in appearance but close observation shows mitotic activity. Local infiltration of adjacent tissues was present in addition to the mitoses (Revised L. W. Histology of the thyroid gland. Medicine Illustrated Feb 1949).

Hurthle cell is a phase in the development of thyroid epithelium. As such it would not represent a distinct anatomical unit but rather a functional change, probably nutritive.

Therefore the derivation of this tumor is obscure. It has been stated that the cell of origin is a thyroid unit, other opinions have maintained that it is a parathyroid derivative. Some believe it to be a stage in the secretory phase of the thyroid epithelium. There are others who state that this type of adenoma is a product of degeneration. According to Symmers, the tumor arising from this cell is divisible into two varieties: (1) an adenoma showing no malignant qualities and (2) a tumor displaying the ability to metastasize thus falling into the category of a malignant neoplasm.¹¹⁶ In a consecutive series of 500 thyroid procedures only one instance of Hurthle cell tumor was encountered by the author.

Case Report. The patient was a 47 year old business executive who was seen for the first time in August 1951. He presented the history of an enlargement in the right side of the neck over a two month period. No toxic symptoms were reported. The significant physical findings were found in the right side of the neck where a visible mass was noted. This mass was partially subclavicular in location and moved with deglutition. The preoperative diagnosis of a right cystic adenoma was made. The patient was prepared for surgery and operated upon. A right hemithyroidectomy was performed without any operative or postoperative complication.

Pathology Report. The surgical specimen was that of thyroid gland measuring 6 by 3.5 cm. It was largely made up of a well-encapsulated nodule the cut surfaces of which were amber and dark red. A rim of normal thyroid tissue surrounded the nodule.

Microscopic study indicated that the nodule had a connective tissue capsule from which vascularized trabeculae penetrated into various directions dividing the tumor into lobules of various sizes and shapes. The cells were roughly polygonal in shape with an alveolar like formation. These cells were large and pale in type. The cytoplasm was eosinophilic containing small oval deeply staining nuclei. The pathologist's diagnosis was Hurthle cell adenoma.

Comment. It was thought that the adenoma here reported was not malignant. However it was further thought that Hurthle cell adenoma should be considered similar to other adenomata of the thyroid in regard to malignancy. Since it is the consensus of opinion among thyroid surgeons that 7 to 8 per cent of thyroid adenomata are potentially malignant this concept should also be applied to the thyroid adenoma under discussion. However, the Hurthle adenoma is so rarely encountered that it is doubted that an adequate series is available to determine the percentage of malignant adenomata in a stated number of cases.

There is a Hurthle cell tumor described which is congenital in origin. The cell derivation of this congenital adenoma as in the adult type is not definitely established. It may find its origin in the thyroid, the parathyroid or another glandular structure. It is mentioned here for completeness of the available existing information on this subject.

10

Thyroid Crisis

FORTUNATELY THE modern surgeon does not encounter thyroid crisis as often as a surgeon did several decades ago. In truth it may be said that many present day surgeons may not witness a complication of this type during their entire professional career. This diminution in the occurrence of thyroid crisis may be attributed to the following:

1. Excellent preoperative evaluation of the patient considered for thyroidectomy
2. Adequate preoperative preparation of the individual to undergo surgery
3. The proper administration of the antithyroid drugs

Although many surgeons complete their surgical training without ever having observed thyroid crisis (thyroid storm) this condition nevertheless is always a possibility and should be anticipated. It is particularly more probable in patients with an initial basal metabolic rate between +80 and 100. Surgery should not be attempted on a toxic thyroid patient until the weight is increasing and the pulse rate is either near normal or is maintained at a steady level. Attention should also be given to the fact that nervousness and emotional instability must be under control and that the pulse rate is near normal and that the metabolic rate is +20 or below. Even when the above criteria are fulfilled the possibility of a thyroid crisis following surgery must be considered. One must also remember that thyroid storms may be a preoperative complication as well as a postoperative one. The most efficacious treatment of postoperative thyroid crisis is to avoid this complication if it is at all possible.

Zondek was the first to describe hyperthyroid crisis and coma.¹ He stated that this syndrome is characterized by marked motor restlessness with uncoordinated movements of the entire body; associated with a rapid rise in temperature and a lack of reactivity on the part of the patient. Increased obtundation may lead to a syndrome which resembles catalepsy or bulbar paralysis.

The clinical picture of thyroid storm according to Means is that of a fulminating increase in the symptoms of thyrotoxicosis. The pulse may rise to 200. The patient is very irritable, often delirious, and at the same time weak to the point of collapse. Coma may supervene and death occur. A prominent feature of storm is hyperpyrexia. In contrast to the usual

preservation of heat in the presence of heightened metabolism in thyroid toxicosis the mechanism breaks down and the temperature rapidly ascends to between 100 and 106 F or more during crisis. It is to be looked upon as in the hyperpyrexia of sunstroke, as due to toxic destruction of the body's organization for eliminating heat. The entire course of thyroid crisis, from the initial symptom to death, may only be a few hours. Recovery is possible, but not the rule.

Lahey called attention to the early signs of an impending crisis.³ These are

- 1 A persistently unexplained increase in pulse rate is a definite indication of a threatening thyroid crisis.
- 2 When a thyroid patient begins to show vague, transient but definite periods of irrationality an impending crisis may be in evidence.
- 3 Vomiting may be another prodromal sign. This indicates the inability of the individual to take in fluids and food and thus to combat the effects of the increased combustion associated with thyroid disease.
- 4 A patient with a definite diarrhea likewise becomes a candidate for a crisis because even though fluid and food be taken, they are rapidly lost as a result of the diarrhea. The metabolic balance is not maintained, hyperthyroidism becomes intensified and the danger of a crisis is imminent.

Croft Jr summarized this state. "A thyroid crisis is a vicious circle of hyperthermia and hypermetabolism. With each degree of elevation of temperature, there is an increase of +12 per cent in the B.M.R. and with each increase in the rate of metabolism there is a proportionate increase in the production of heat by the body."⁴ Under the circumstances the patient burns up his tissues until he is exhausted.

Theories of Thyroid Crisis

As in many problems associated with the physiodynamics of disease the exact cause of thyroid crisis is unknown. With this uncertainty no general agreement as to etiology can be postulated. This has resulted in many theories according to the experience of investigators who have studied this entity.

Hergot in 1940, reviewed the various theories promulgated by Europeans. There was among the eccentric theories quoted one by Just. This author stated that the rise in temperature (in crisis) is due to operative trauma in that disintegration of proteins takes place and leads to irritation of the heat center. Hergot further reveals that many authors up to

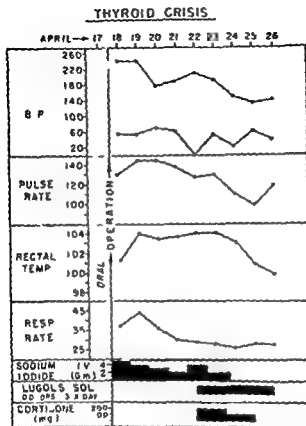


FIG. 4. Clinical chart of a 44-year-old Negro female who developed a postoperative thyroid crisis. This patient was treated preoperatively with iodothiouracil (combination of iodine and thiouracil). She was given mercaptoimidazole irregularly from July 28, 1950, to September 1951. On September 21, 1951, she was given iodothiouracil (100 mg t.i.d. dose increased later). The B.M.R. was +25 in April 1957 when she was admitted for surgery. On April 18, 1957, a subtotal thyroidectomy was performed. The above chart shows the temperature, pulse rate, respiration, and blood pressure changes during the immediate postoperative days. This patient was treated with cortisone, intravenous glucose plus sodium iodide, vitamins, sodium amylal, sedation and oxygen. In addition, the hyperpyrexia was combatted by means of saline lotions, cold packs, ice water enemas, cooling fans, and antibiotics. The patient was discharged from the hospital 14 days after operation. Patient of Seven and Perloff.¹⁰

the writing of his article believed that crisis is due to postoperative hyperthyroxemia. This hyperthyroxemia may be provoked by many factors. Among the provocative causes he mentioned are:

1. Operative manipulation of the thyroid gland which mechanically increases thyroxine in the blood, and

2 Reflex influence on the hormonal secretion by injury to adjacent nerves

Bier (quoted by Herget) assumed that hyperthyroid coma actually constitutes a hypothyroxemic shock due to lack of active thyroid hormone. Sauerbruch (quoted by Herget) attributes crisis to a sudden reduction in the hormone concentration after subtotal resection. This leads to a disturbance of endocrine and nervous equilibrium producing postoperative crisis. Kappis (quoted by Herget) stressed a shift in the ionic equilibrium toward the acid side as a participating factor in the causation of crisis.

The thymus has been accused as the etiological agent in crisis by Kocher (quoted by Herget). He observed thymic hyperplasia in more than 50 per cent of deaths from Basedow's disease. Garre and Borchard elaborated upon this thought by stating that it is produced in patients with a persistent thymus. This gland acts on the heart and produces an increase in the effect of thyroid secretions. Garre (quoted by Herget) was able to cure patients with Basedow's disease by extirpation of the thymus. Foss and associates studied this problem and concluded that "while so called thymic death does not resemble in many respects death from thyroid crisis the majority of patients dying in crisis will be found, at autopsy, to have a persistent and hypertrophied thymus".

Herget likened crisis to an allergic or anaphylactic reaction. He believes that crisis might be prevented in the same way as the anaphylactic shock of serotherapy might, and can be avoided by preliminary injection of a small desensitizing quantity of serum.

McGregor thought that an underlying polyglandular stimulation in certain adolescents resistant to iodine was a factor.⁷ Thus he stressed preoperative radiation of the pituitary and adrenal glands with satisfactory results. In keeping with this endocrine concept Nash called attention to the antuitary.⁸ He maintained that thyroidectomy causes the antuitary to produce an increase of thyrotrophic hormone besides other hormones. This postoperative outpouring of potent antuitary substances may induce the so called thyroid crisis. "one or more of the hormones having probably a greater influence in this direction than the others."

Further thoughts on the relation of the thyroid gland to other glands attracted interest to the adrenal. Levy was the first investigator to demonstrate that injections of adrenalin caused an action current in the thyroid gland.⁹ In addition, he pointed out that thyroid secretion renders the sympathetic nerve endings more excitable when acted upon by adrenalin. It had further been revealed that as a result of the administration of adrenalin glycosuria in animals disappeared after excision of the thyroid. The

glyco uria reappeared however when the animal was fed thyroid extract. There is known to be a reciprocal inhibition between the thyroid and the pancreas on the one hand and between the pancreas and chromaffin system on the other.¹⁰

The adrenalin test of Goetsch¹¹ was based on the work of Levy who showed that in hyperthyroid dogs the sympathetic nerve endings were abnormally sensitive to small dose of adrenalin. Further evidence to support the adrenal thyroid relationship was found by Goetsch and Ritzmann.¹ Hyperadrenalinism whether due to psychic influences, anoxemia or other causes may exert some influence in the precipitation of thyroid crisis. Prevention therefore of both disturbing stimuli and anoxemia is essential to the well being of the thyrotoxic patient. The evidence offered by Goetsch and Ritzmann indicated that adrenalin should not be given in thyrotoxicosis.¹² Additional studies by Maddock and his associates¹⁴ increased the evidence in favor of the adrenal theory. Substantiating the relationship between the adrenals and thyroid crisis. Rees employed spinal anesthesia in the treatment of thyroid crisis.¹ This procedure was offered on the basis that spinal anesthesia temporarily denervates the adrenal glands. The observations by Brice and Reid brought forth additional clinical evidence regarding the ergotamine ergotamine adrenalin relationship.¹⁶

In 1936 Lahey reiterated the hypothesis that hyperthyroidism was allied to hyperiodinism.¹ The work of the Lahey Clinic chemist Perkin on blood iodine and its relation to toxic thyroid states is widely known. He found that in normal individuals thyroxine is confined to the thyroid gland whereas in toxic states increased thyroxine is found circulating in the blood. The low amount of iodine in the thyroid tissue represents a state in which the thyroxine when produced in an excessive amount is rapidly discharged from the thyroid. Thus when patients improve or are relieved of their hyperthyroidism there is an immediate increase in the amount of iodine stored within the thyroid gland. The facts fit most satisfactorily into the theory of hyperiodinism representing hyperthyroidism.

Other concepts of thyroid crisis have been offered for consideration. Ewald¹⁵ ascribed post-operative crisis to a sudden flooding of the organism with thyroid secretion but he suggested that perhaps it was really due to sudden deprivation of thyroid secretion instead. The theory of Letchford¹⁹ stating that crisis was due to thyroid failure appears to have had little basis in fact. Pedersen¹ studied the work of Schneider on the serum sodium content and this was not corroborated. It was apparent to Pedersen¹ that determinations of the serum sodium have no value in relation to hyperthyroidism. Maddock and his associates thought crisis might be ex-

plained by ionic disturbance. However their experiments led them to conclude that searches for abnormalities in inorganic ion concentrations in blood were unrevealing.

All the theories advanced as to the etiology of thyroid crisis have not satisfactorily answered the numerous questions associated with this phenomenal syndrome. In the quest for the answer to some of these questions many investigators have been attracted to the role of the liver in thyroid disease.

The Hepatothyroid Relationship

The correlation between the largest gland in the human body, the liver, and the potent cervical endocrine gland, the thyroid, was not suspected until 1905. Since then however, pathologists and laboratory investigators have called attention to pathological changes in the liver associated with hyperthyroidism. Both experimental and histological evidence was offered to associate the liver with thyroid dysfunction. In spite of all the evidence presented clinicians and surgeons ignored the proffered benefits derived from the laboratory and theorized as to the etiology of thyroid crisis.

This stream of experimental pathological studies began in 1905. Schryver observed a greater degree of autolysis in the livers of thyroid fed animals than in the livers of control animals after 24 hours.¹ Farrant found that in thyroid fed cats and rabbits in which a modified picture of exophthalmic goiter had been produced exhibited at postmortem examination in addition to other changes fatty degeneration of the liver most marked around the center of the lobules.² In the same year, Cramer and Krause noted that excessive thyroid administration resulted in glycogen depletion of the liver. Kuriyama studied the effect of thyroid feeding on white rats and found that within 3 to 5 days practically all of the animals exhibited a decreased glycogen content of the liver.^{3, 4} Both Hashimoto⁵ and Goodpasture^{6, 30} (1921) fed albino rats and rabbits thyroid substance in an endeavor to produce histological changes in the myocardium. To their surprise both produced parenchymatous change in the liver. Goodpasture reported a clinical case of hyperthyroidism which exhibited at autopsy progressive atrophic cirrhosis of the liver with numerous vacuolated nuclei suggesting glycogen depletion. Haban (1935) was able by thyroid feeding to produce necrotic changes in the livers of cats and rabbits.³¹ Moreover he observed a total depletion of glycogen content. The findings were confirmed experimentally by Zeldenrust and Van Beek.³²

Enough additional scattered reports have been recorded in the literature

to establish a definite thyrohepatic relationship Cameron and Karunarine published an extensive study on this relationship based on 30 cases.³³ The investigators attached no special significance to their studies. They considered the pathological finding of necrosis as evidence of a severe toxemia based on atrophy and cirrhosis. Roosevelt postulated an hypothesis that in the presence of thyrotoxicosis a toxin is elaborated which acts on the liver because of the detoxifying function of that organ.³⁴ Parturier and Delerue stated that 30 per cent of all patients with hepatic disease present signs and symptoms attributable to the thyroid gland.³ They observed from clinical observation that the effect of the thyroid on the liver is less marked than the effect of the liver on the thyroid, stating:

Thyroid function is unaltered only when hepatic function fails.³⁵ Rome called attention to the frequency with which thyroid failure is complicated by various types of hepatic dysfunction.³⁶ An analysis for toxic thyroid disease was made by Beaver and Pemberton of 107 autopsies at the Mayo Clinic.³⁷ From their survey they believed that in most instances the lesions in the liver appeared to be an integral part of the syndrome of exophthalmic goiter and to be due directly to thyroid intoxication.

More specific elucidation of the pathological changes in the liver due to thyroid disease was forthcoming. Weller described the usual liver lesion as an interlobular fibrosis with lymphocytic infiltration.³⁸ Among the reports published on the study of liver damage in patients who died of thyroid crisis is that of Youmans and Warfield.³⁹ They reported liver damage in 4 and jaundice in 3 of 5 patients who died in crisis. Asmann distinguished a type of hyperthyroidism associated with a rapidly lethal outcome.⁴⁰ In these cases the more severe conditions passed into acute atrophy of the liver. Mahorner reported an interesting case of exophthalmic goiter in which jaundice was a prominent finding.⁴¹ The fact that it disappeared less than a month after thyroidectomy suggested to him that liver damage can be caused by thyrotoxicosis and that adequate therapy can restore the liver to normalcy. Foss and associates in a study of 11 cases of thyroid deaths found but one normal liver in the cases of true crisis.⁶

The above literature describing hepatic disorders in thyrotoxicosis strongly indicates a definite relationship between these two organs, the liver and the thyroid. Hence it can be appreciated that both the experimental and pathological evidences previously enumerated indicate a direct relationship between toxic thyroid disease and liver damage. Which ever one is accepted as the causative factor is not of primary concern. Investigators appear more interested in discovering some method by which the state of the thyroid patient can be estimated in terms of the hepatic factor. For this reason attention has been given to formulating laboratory tests on liver function in the thyroid patient.

Laboratory Tests on the Liver in Thyroid Disease

Possessing a tremendous reserve capacity, the liver has the ability to function in the presence of extensive parenchymatous damage. For this reason an efficacious test of hepatic efficiency must of necessity be most sensitive. In the pursuit of the ideal test many procedures have been offered. Because the maintenance of a normal blood sugar is a most important function of the liver it is preserved to the very end.⁴ Of the tests on carbohydrate function the galactose tolerance test has been most favored.⁴ Judd considered that the methods for detecting hepatic injury by testing sugar metabolism were so unreliable as to suggest that they affected only the reserve capacity of that organ.⁴³

Urea is formed in the liver and uric acid is presumably formed and destroyed in that organ. Thus it might be expected that blood urea and uric acid determinations would be a secure calibration of early hepatic dysfunction. However such determinations are of little value until liver damage is far advanced.⁴

Other studies on hepatic function involved tests for cholesterol. The normal values for blood cholesterol are usually 200 mg of cholesterol and 100 mg of cholesterol esters per cent. Formerly variations of from 30 to 50 per cent in the ratio were considered normal but now it is believed that the free cholesterol in normal individuals is usually not greater than 30 per cent of the total.⁴ Changes in the ratio are more important than changes in the concentration of total cholesterol since the esterification of cholesterol esters from cholesterol and high fatty acids is accomplished in the liver. Pickhardt and his associates⁴⁴ found the cholesterol of the blood serum to be a valuable index of hepatic reserve, as did Sperry.⁴ Other observers however have stressed the ester cholesterol.⁴

More specific liver function tests were studied in attempting to evaluate the hepatic status in hyperthyroidism. Serum protein values of thyroid patients have been examined by several investigators. Bartels found the total serum proteins below normal in 63 per cent of the patients he studied.⁴⁵ This protein depletion was noted when the patients were first seen or as in 37 per cent of the cases after 10 days of therapy.⁴⁶ Bartels observed a definite relationship between the level of total serum protein and the severity of the hyperthyroidism. This necessitated surgery in stages before the days of the antithyroid drugs. Further studies on the inorganic sodium content of blood serum in hyperthyroidism were made by Pedersen.⁴⁷

The importance of iodine and its relationship to hyperthyroid states has been previously mentioned. With this association in mind most interesting studies have been evolved about the blood iodine test. Data have been accumulated which point to the liver as a factor in iodine metabo-

him⁴⁷ Experimental evidence has been offered to indicate that the liver is involved in normal iodine metabolism. Maruno has stated that iodine is excreted with bile.⁴⁸ Yuzuriha maintains that the reticuloendothelial system is concerned with the removal of iodine from the blood.⁴⁹

With the evidence as a background De Courey attempted to correlate elevated blood iodine with disturbed liver function.⁵⁰ This investigator pointed to the liver as a potent factor in the regulation of blood iodine. He speculated in the absence of proof that the activity of the reticuloendothelial system might play an important part in iodine metabolism. He has tentatively assumed that when the iodine content of the blood is below 100 $\mu\text{g}/100\text{ ml}$, operation can be done with reasonable safety as far as the liver status is concerned.⁵¹

Of all the tests employed in studying hepatic function in thyroid disease the most satisfactory procedure is the Quick hippuric acid test of the detoxifying function. This method has been employed extensively and successfully at the Lahey Clinic and by Boyce.⁵² Boyce used this test in 130 cases of thyroid disease.⁵³ He concluded that hepatic dysfunction in hyperthyroid disease is more frequent and more serious than was generally realized. He postulated that the progression or regression in function as exhibited by serial Quick tests corresponds to clinical improvement or lack thereof. The degree of hepatic dysfunction is usually related to the clinical severity of the disease and to the degree of toxicity as exhibited by the basal metabolic rate.⁵⁴ Improvement in liver function occurs in patients who respond clinically to adequate preparation for operation. This he believes to be a useful test in evaluating the results of therapy. In the employment of the Quick test it is important to know that its greatest value is derived when it is used serially. When it is used in this way it is possible to state that a patient is a good or bad risk from the hepatic standpoint. It is possible to determine from the response to treatment as expressed by this test whether the risk has improved, remained stationary or has become worse.⁵⁵

From all the evidence thus far presented it is evident that many isolated studies have pointed to the importance of liver function in toxic thyroid disease. The various tests employed indicate that hyperthyroidism has a damaging effect on the liver. It is well to mention here that the cephalin flocculation test is not satisfactory for our purposes.

Clinicopathological Evidence for the Hepatothyroid Concept

In the presence of the universal and frequent experimental results clinicians were slow to grasp the full significance of the laboratory evi-

dence in support of the hepatothyroid association. The liver and thyroid have a common anatomic relationship in that both are glands. Experimental physiopathologists, and later clinicians, have discovered a closer interrelationship between these organs than would appear from this casual anatomic fellowship.

It is only within the last decade that the literature has contained clinical references to the hepatothyroid correlation. Surgeons now recognize that the liver in thyroid disease is of significant importance. Many of them have believed that deaths occurring in hyperthyroidism are chiefly liver deaths. Boyce likens thyroid crisis to a "liver shock" type of death, which sometimes follows surgery of the biliary tract.⁴ Connell believed that the syndrome of rapid hyperpyrexia death occurred only after biliary tract surgery. However, he soon abandoned this view and believed it could occur in many other operations.

Hyperpyrexia death may follow operations in badly prepared patients. It has been allied to thyroid crisis because the clinical picture closely simulates the syndrome seen in untreated or mistreated toxic thyroid disease. As to the cause of this calamity of thyroid crisis, Boyce suggests that the toxic overstimulated metabolism results in combustion of the protective glycogen of the liver beyond the degree of safety.⁴ When this point is reached there develops sudden and extreme hyperpyrexia, an almost uncountable pulse, vomiting and diarrhea. Restlessness may supervene and may pass into delirium, coma and death.

Other authorities have concurred in the thyrohepatic relationship. The two Criles,³ and later Dinsmore^{5, 6} have remarked that liver failure is the most common cause of thyroid delirium, mental confusion and death in thyroid crisis.

The younger Crile expressed this concept as a problem of hepatic failure and metabolic exhaustion.⁴ He emphasized the possibility of jaundice. Visible jaundice may be present in some cases whereas in others repeated determinations of icteric indices may fail to show any increase above normal level. If the icterus index is not elevated there is no way of relating the syndrome to the liver and hence it is called metabolic exhaustion. If the presence of jaundice is noted it is classified as hepatic failure.^{1, 4}

Lahey reported that he was more and more certain that deaths due to hyperthyroidism were chiefly liver deaths.⁶ He has adduced in support of this thought not only the clinical picture of crisis but the efficacious utilization of intravenous glucose to combat the excessive combustion resulting from hyperthyroid states. He believed that with excessive hyperthyroidism goes excessive combustion and when fluid and fuel intake is inadequate to meet this excessive degree of combustion progresses to auto

combustion occurs with exhaustion of available glycogen and diminution of the glycogen reserve in the liver.⁵¹

Additional studies have substantiated the close relationship between the liver and hyperthyroidism. An intimate association between thyroid crisis and functional changes in the liver was suggested by Lord and Andrus on the basis of their study of the plasma prothrombin level in 36 patients with hyperthyroidism.⁵² Frazier and other surgeons at the University of Pennsylvania published important results on the therapy of thyroid disease as directed to the liver factor.⁵³⁻⁵⁵ Studies by Bartlett confirm and emphasize the importance of liver damage in toxic thyroid disease.⁵⁶⁻⁵⁹

Early studies on the pathological picture of the liver in thyroid disease originated in the experimental laboratory. With the influence of adrenalin in thyroid disease as a guide, Perrazzo in 1934 was able to produce advanced fatty degenerative changes in the liver.⁶⁰ At that time this finding was considered to be the major pathological lesion observed in many fatal cases of hyperthyroidism. Perrazzo accomplished this experiment by the intravenous injection of moderate doses of adrenalin.

Shaffer in a study of the livers from 24 fatal cases of toxic thyroid disease found a loss of liver weight, fatty infiltration, cirrhosis and lymphocytic infiltration in the periportal region often associated with patchy fibrosis.⁶¹ Webster and Cheney have shown that when rabbits are fed a diet rich in cabbage a marked degree of goiter results.⁶² Examination of these thyroid glands showed a considerable degree of hyperplasia which was considered to be compensatory. According to Marine, a cyanide is the active principle in cabbage.⁶³ Thyroid hyperplasia and even exophthalmos may be produced in young rabbits by the injection of cyanides which greatly lower the oxidation in body tissues. Cyanide is toxic to the liver. Herein may be the cause for the hepatic picture produced by the investigators analogous to the findings of Shaffer.

Boyd has summarized the major pathological hepatic picture in thyroid disease stating: "There is no constant pattern in the liver lesions but they are essentially congestion and degeneration. Fatty degeneration is extremely frequent. There may be acute necrosis, both focal and central. Subacute toxic atrophy may occur with the development of cirrhosis and nodule formation."

Anoxia and Hepatic Disease

The increased metabolism of the thyroid patient has been indicted for the faculty with which these individuals develop anoxia. Several excellent monographs have been written demonstrating the pathological changes wrought in the liver subsequent to anoxia. Under such conditions of hepatic

anoxia, the damaged liver appears to accelerate the thyroid gland to hyperactivity. In a situation of this type a mutual distortion of hepatic and thyroid function results. Anoxic damage consumes the hepatic protein elements and the stored glycogen. These debilitating factors leave a cadaveric organ which is depleted of all its reserve capacity. In this state an additional glycogenolytic process as demanded by thyroid hypermetabolism cannot be satisfied. This is the basis for liver exhaustion and thyroid death.

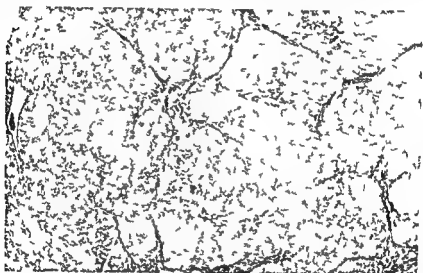


FIG 46 Photomicrograph (20 X) showing fatty degeneration of the liver giving the picture of fatty portal cirrhosis. There is no constant pathologic pattern in the liver lesions of hyperthyroidism but there are essentially congestion and degeneration. Fatty degeneration is frequent. Other histopathologic changes may be acute liver necrosis, both focal and central. Subacute toxic atrophy may occur with the development of cirrhosis and nodule formation.

Experimental evidence on the extraordinary sensitivity of thyroid fed rats to want of oxygen was recorded by Asher and Duran in 1920⁶⁹. They showed that hyperthyroid animals could not tolerate even minor degree of anoxia. Two years previously, Streuli and Asher found the converse to be true. Thyroidectomized rats were able to tolerate a lack of oxygen which brought normal animals to the point of death by asphyxiation.⁷⁰

More recent studies have revealed the effects of anoxia on the liver in hyperthyroidism. Hepatic distress subsequent to want of oxygen is logical. Liver cells are closer to a phyxiation than other cells because only 20 per cent of their blood supply is supposedly arterial.⁷¹ Reinwein and Singer led one to assume that increased oxygen demand by the liver in a hyper-

thyroid state leaves a narrow vital margin of safety, which is easily destroyed.⁷ In the same trend of thought McIver has shown that the liver is particularly susceptible to injury under conditions of hyperthyroidism.^{7a}

More recent experiments by McIver and Winter elucidate the effect of anoxia on the liver during artificial hyperthyroidism in rats.⁴ These investigators studied the behavior reaction of hyperthyroid and normal animals when exposed to low oxygen atmosphere (11 per cent). The normal animals showed no signs of acute distress except for a slight increase in respiratory rate. The hyperthyroid animals were restless and apathetic. They studied 26 rats, 17 of which had received injections of crystalline thyroxine. Nine of the 17 hyperthyroid rats died after varying periods of anoxia. The first 2 hours in the low oxygen atmosphere seemed to be the most critical for the hyperthyroid rats.

The effects produced by lack of oxygen were similar to those of glycogen imbalance. The studies of McIver confirmed some aspects of the work produced by Lewis and his associates.^{7b} In their studies on the role of the adrenal cortex in acute anoxia they confirmed the previous conclusions of Evans.^{8, 7} All showed that hepatic glycogen tends to fluctuate in rats exposed to low atmospheric pressure.

Knowing *de facto* that deleterious damage occurs in the liver due to the factors presented, pathological studies have confirmed definite anatomic alterations in the liver. Scholars concerned themselves with this problem as early as 1913. Farrant produced histological changes in the liver by administering thyroxine.⁹ Similar results were produced by Gerler who employed large and even fatal doses of thyroxine.⁴ McIver attempted in his experiments to use nonlethal doses. The amount employed was merely sufficient to produce a hyperthyroid state. In this way he hoped to avoid the pathological changes in the liver caused by overdosage. His plan was to produce alterations in hepatic tissue by anoxia in the hyperthyroid animals. His subjects were all healthy and free from disease. This healthy state was important because Haban in studying the effects of crystalline thyroxine injections on the liver found tissue change only when some intercurrent infection was present.⁸⁰

The most lucid study on the histological pathology of the liver was made by McIver in his experiments.⁵ He has shown that the pathological material from the rats killed after receiving crystalline thyroxine in nonlethal doses failed to reveal any notable histological abnormalities of the liver. However when the cells were compared with those of normal well fed rats the cells in the livers of thyroxine treated rats were more homogeneous and compact. The appearance of the cells however did not differ essentially from the hepatic cell of a starved animal. McIver attributed this analogy to the fact that hepatic glycogen was diminished markedly

Anoxic changes have been recorded in hyperthyroid rats. As might be expected, the lesions in animals that died or were killed after short exposures to oxygen deficit were not advanced. Those changes consisted of fatty changes, vacuolization of the cells and engorgement of the blood vessels. In the animals exposed for longer periods the degenerative changes were severe and widespread. A summation of the pathological findings may be stated as:

- 1 Necrosis most pronounced around central veins
- 2 Marked engorgement of the sinusoids especially in the vicinity of the central veins
- 3 The cell outlines were often lost
- 4 The cells in the areas of degeneration showed an affinity for eosin
- 5 Pyknotic nuclei were found to be associated with the loss of cell boundaries

From the pathological data already presented the noxious effect of anoxia upon the liver is obvious. It is further evident that in the patient with hyperthyroidism every precaution is essential in order to avoid the complications associated with a low oxygen tension. This problem gives rise to the choice of anesthesia for a toxic thyroid patient who is a potential candidate for anoxic anoxia. For this reason Colcock has stressed the point of anesthesia. Nitrous oxide was abandoned because too little oxygen (usually only 10 per cent) was available to the thyroid patient whose oxygen demand was 2 to 3 times that of the average patient.⁸¹ Avertin enjoyed popularity and was frequently employed with nitrous oxide. Avertin a respiratory depressant has in the experience of Cole and Brunner, occasionally increased the toxicity in patients with severe hyperthyroidism.⁸ These problems on anesthesia brought to light the rationale and use of oxygen in the postoperative treatment of hyperthyroidism as well as the value of oxygen during thyroidectomy.⁸²⁻⁸⁴

Comments and Conclusions on Thyroid Crisis

From a literary review it can be stated that many surgeons and investigators have studied the role of the liver in thyroid disease. Of all these, several have intimated and few have definitely incriminated the liver as the seat of distress in thyroid crisis. This review of the subject leads one to believe that the liver is in some way, the organ to be indicted as a potent factor in the pathogenesis of thyroid crisis.

Among the reasons for this belief are:

- 1 The clinical picture of crisis closely simulates exhaustion resulting from hepatic hyperpyrexia

- 2 Experimental evidence and the morbid anatomical findings indicate the close association between hyperthyroidism and the liver
- 3 Boyce's results with the Quick hippuric acid test of liver function have been offered as proof of liver damage occurring as the result of thyroid disease
- 4 The physiological imbalance and pathological changes in the liver due to anoxemia have been established. Anoxia in hyperthyroidism is common knowledge
- 5 The interrelationship between hyperadrenalinism, hepatic glycogenolysis and the experimental production of toxic thyroid signs by injections of adrenalin have been emphasized

The premise of this discussion therefore is that the most important organ exclusive of the thyroid itself concerned in the production of thyroid crisis is the liver. Physiological failure of this organ will result in so-called thyroid death. This conclusion is reached following clinical observation, experimental data, laboratory function tests and objective findings as revealed by pathological anatomy.

The causative or exciting agents in the production of hepatic imbalance may be multiple or a combination of several. Of all the phases discussed on this aspect of the subject the most plausible possibilities are hyperadrenalinism and hepatic anoxia. These states either alone or acting synergistically in the presence of hyperthyroidism may be the fundamental destructive influence in the evocation of crisis. Hyperadrenalinism may be the activator in depleting the liver of its available glycogen. In this state of insufficiency the hepatic anoxia resulting from increased hypermetabolism produces the lethal blow which precipitates crisis and the eventual hyperpyrexia, thyroid death.

Attention is called especially to anoxia. It is strongly believed that the acute pathological lesions found in the livers of patients dying from hyperthyroidism are the result of anoxia. This is a problem of clinical importance since the occurrence of anoxia in hyperthyroidism is commonly known. Especially is this of great concern in the production of postoperative crisis when tracheal obstruction, pulmonary edema or other complications may interfere with adequate pulmonary aeration.

One is not unmindful of the fact that the liver may be merely a solitary reflection of a generalized somatic picture. Anoxemia may affect all the organs in the body in the production of crisis. The liver however has been stressed in hyperthyroidism because its normal physiology and pathological physiology can be tested with ease and because this organ is subjected to routine examination at autopsy. That physiological discord in crisis is revealed in other organs and tissues of the body is appreciated. Even though this is known it is believed that the fulminating picture of

crisis and death occurs only when the liver has been burdened beyond its ability to compensate for the demands required under the stress and strain of thyrotoxicosis.

On the basis of all the proof offered as to the role of the liver in hyperthyroidism, a notation on preoperative preparation is not amiss. Fortification of the liver should be of primary concern. This should include a liberal carbohydrate diet, glucose by mouth or by vein, (preferably supplemented by decholin), a definite proportion of protein in the diet, vitamins and blood transfusions. In this regard Lahey has stated: "There is one point regarding the treatment of thyroid crisis and that is the need to give these patients fluid and glucose constantly and not intermittently. There is a tendency to be intermittent. This is unwise since it leaves periods during which the excessively activated metabolism will still consume the liver reserve. It is necessary in patients with thyroid crisis to give them fluids and glucose quite constantly throughout the entire day if one wishes to extricate them from these serious thyroid states."¹⁷

The topic of preoperative preparation brings to mind the diversity of opinion as to multiple stage operations in thyrotoxic patients. Decades ago those patients with toxic goiter known to be recalcitrant to iodine therapy and considered unfavorable operative risks were subjected to multiple stage operations. It is felt that the beneficial effects of this procedure were not due to the simplicity of the operation. Credit must be given to the fact that the respite between stages gave the patient a preoperative regimen on more than one occasion. This preparation directed toward "building up the patient" inadvertently fortified the liver against a future thyroid crisis. In keeping with this thought it is believed that multiple stage procedures were not the answer to the prevention of crisis but rather that rehabilitation of the liver was the *sine qua non* of prophylaxis.

One of the purposes of this discussion is to bring to the attention of the surgeon that prophylaxis against thyroid crisis is preferable to therapy after the syndrome has developed. Fortunately crisis is rarely encountered today. With this idea before the reader, the writer has accentuated the value of preoperative rehabilitation of a liver suspected of dysfunction and of fortifying an apparently normal liver. In the preoperative care of a patient suspected of being a candidate for thyroid crisis the following is a recommended regimen:

- 1 Complete bedrest
- 2 Lugolization
- 3 Sedation (phenobarbital, bromides)
- 4 Propylthiouracil is administered until BMR is near normal
Lugol's iodine or organidin is given simultaneously

- 5 Oxygen tent to combat anoxia and hyperthermia if necessary. By placing a patient in a tent an evaluation of the pulse can be estimated. If the patient is perturbed by the tent he is not psychologically prepared for operation.
- 6 Glucose intravenously plus amino acids and vitamins (for three days)
- 7 Blood transfusion to combat anemia
- 8 Cardiac therapy when indicated
- 9 The patient's pulse is strongly considered and treated

The hyperthyroid individual is treated as a psychosomatic entity. The best guides to the patient's response to therapy and calibration as to operability are

- 1 The patient's mental attitude
- 2 The fall and maintenance of a normal or near normal pulse rate
- 3 A consistent fall and maintenance of a lowered basal metabolic rate

It is believed that in strengthening the role of the liver in crisis future clinical and laboratory investigators may find the solution to this intricate problem.

In conclusion it may be reiterated that clinical observation has suggested a possible hepatic basis for the pathogenesis of thyroid crisis. The physiologist and experimental clinician have presented evidence substantiating this belief. Both gross and microscopic hepatic studies have augmented the proffered evidence. The liver therefore when distressed due to glycogen depletion may be accused as the death-producing factor in accelerated hyperthyroidism. By promulgating this concept it is hoped that interest will be stimulated toward that organ. From this stimulus some future investigator may confirm or deny the master role of the liver as the major etiological agent in the production of thyroid crisis.

Addenda

A. R. Hunter of London has reported the beneficial effects of chlorpromazine as an aid in cooling the patient in thyroid crisis. Following thyroidectomy one of his patients went into thyroid crisis. Her temperature rose to 103°F (40.6°C) and the pulse rate was 200. Twenty-four hours after surgery it was apparent that a thyroid crisis was developing. The patient was packed in ice and was in addition given a test dose of chlorpromazine 25 mg orally followed by 50 mg 4 hours later. A further 50 mg dose was given every 8 hours during the subsequent 72 hours. Her temperature fell steadily. Subsequently her condition improved steadily but the administration of chlorpromazine was continued. The patient is

covered. During the administration of the drug the patient had ice bags placed under each axilla, over the abdomen, and both groins. The patient was placed in an oxygen tent. The author stated that he believed that the essential problem in thyroid crisis was to reduce the excessive metabolic rate. He believed that in the past there had been no completely effective method of doing this and for this reason the mortality in crisis had been very high. In the case he reported the combination of cooling, with the prevention of shivering by the administration of chlorpromazine, seemed to answer the problem.⁶¹³

Hyperthyroidism and Myasthenia Gravis

On infrequent occasions myasthenia is an associated symptom of hyperthyroidism. Bartels of the Mayo Clinic stated that the incidence of combined hyperthyroidism and myasthenia gravis is less than 1 in 3 000 hyperthyroid patients.⁸

Thorn and Eder have summarized the various types of muscular dysfunction which may complicate hyperthyroidism as follows:¹¹

- 1 Exophthalmic ophthalmoplegia
- 2 a Acute thyrotoxic myopathy
- b Thyrotoxic periodic paralysis
- c Chronic thyrotoxic myopathy
- 3 Myasthenia gravis with hyperthyroidism

The purely thyrotoxic myopathies always improve as the patient is restored to an euthyroid state. Since the control of myasthenia gravis invariably requires additional therapeutic measure, its recognition as a complication of hyperthyroidism is important. The reported cases suggest that the control of the hyperthyroidism may have a variable effect upon the coexistent myasthenia gravis in some cases relieving and in others intensifying the muscular weakness.

The cause of myasthenia gravis is unknown but the defect appears to be at the myoneural junction with a failure of passage of impulses from the nerve to muscle probably resulting from a deficiency of acetylcholine. Daily administration of maintenance doses of neostigmine or pyridostigmine bromide orally is usually successful in alleviating the muscular weakness. Since thyrectomy introduced by Blalock in 1939 has been successful in relieving symptoms in certain cases of myasthenia gravis partial extirpation of this organ may be performed.⁸

The manifestations of thyrotoxic myopathy and myasthenia gravis are quite similar but they can be differentiated. While both may give rise to external ophthalmoplegia ptosis is rarely seen in hyperthyroidism. Like wise, dysphagia and dysphonia do not occur in hyperthyroidism but are

frequently present in myasthenia gravis. The greatest aid to the diagnosis of myasthenia gravis lies in the response to the intramuscular injection of neostigmine.

Improvement in the symptoms of myasthenia gravis with the onset of



FIG 47 Patient with myasthenia gravis. (1) Ptosis the most common symptom of myasthenia gravis frequently associated with limitation of extraocular movements (2 3 4) In this patient left ptosis is accentuated on left lateral gaze (2) The left lower lid elevates slightly on right lateral gaze (4) Characteristically visual acuity accommodation and pupillary responses are unimpaired Retraction of upper right lid seen here is an uncommon development Effects of neostigmine are shown in picture 5 An injection of neostigmine was given and in 15 or 20 minutes the patient got up out of bed walked around raised her arms and was almost normal (Walsh F B Myasthenia gravis and its ocular signs *Tr Am Ophth Soc* 41: 556 1943)



FIG 43 (top) Photomicrograph demonstrating multiple lymphoid germinal centers in the thymus gland of a patient with myasthenia gravis. The lower photomicrograph is that of a normal thymus gland presented for comparative study. Approximately 6×100 .

hyperthyroidism may occur in some patients. Relief of the patient's symptoms may result if both a thyroidectomy and a partial thymectomy are performed.

The course of myasthenia gravis is often characterized by remissions

but recurrences and progression ultimately occur in the majority of cases. Although prolonged spontaneous remission is the exception, this must be considered in evaluating any form of therapy for myasthenia gravis.

It is interesting to note that Merten¹ of Germany has cured several cases of myasthenia gravis by surgical denervation of the carotid sinus. He has preceded his operative denervation with a therapeutic test consisting of novocaine nerve block of the area.⁶⁰⁴

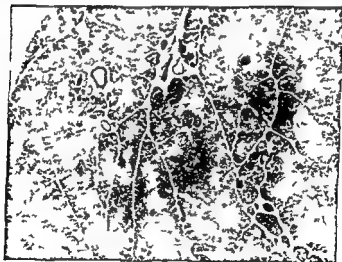


FIG 48 (*top*) Photomicrograph demonstrating multiple lymphoid germinal centers in the thymus gland of a patient with myasthenia gravis. The lower photomicrograph is that of a normal thymus gland presented for comparative study. Approximately 6×100 .

hyperthyroidism may occur in some patients. Relief of the patient's symptoms may result if both a thyroidectomy and a partial thymectomy are performed.

The course of myasthenia gravis is often characterized by remissions

The β isotope in organic iodine contains a large dose of radiation which is readily delivered to the overactive thyroid cells. If the dose is sufficient actual necrosis of the thyroid cell can result.

The normal thyroid gland picks up about 20 per cent of an ingested dose of radioiodine while the gland of the patient with hyperthyroidism will collect about 80 per cent. In myxedema little or none is collected by the gland. Both beta and gamma rays are emitted by radioactive iodine. The beta rays have a maximum range of only a few millimeters and radiation can thus be confined almost exclusively to the tissue holding the radioactive isotope. Collection of radioiodine by the thyroid usually occurs within a few hours. What is not absorbed is excreted readily by the kidneys.

The principal isotopes used are I^{130} (with a half life of 12 hours) and I^{131} (with a half life of 8 days). Fifty per cent of the total radiation dose from I^{130} is delivered in the first 12 hours and 90 per cent within 36 hours. Determination of the amount required by a patient is partly guess work since an estimation of the weight of the gland must be made in calculating dosage. Generally 5 mc to 25 mc will be effective. The calculated dosages in which internal radiation has been successful are from 500 to 2000 roentgens which agree with figures for external radiation generally used. Certain prerequisites for successful treatment have been advised. For example the patient should have received no previous iodine for at least one month, he should be available for close follow up and he should be given routine iodination with Lugol's a few days after his original dose of radioiodine. Not all radiologists agree that Lugol's is necessary in every case. Contraindications to radioiodine include large goiters which require surgery to relieve pressure symptoms, pregnancy and kidney disease.

Effects of Radioactive Iodine

Within a few days after an ingested oral dose of I^{130} the gland becomes firmer and slightly tender. The beginning of relief of symptoms is variable, being from a few weeks to a few months. Some proponents of internal radiation claim that an 80 per cent cure rate is possible. In view of the fact that a very large number of patients treated with the β isotope have not been reported in the literature this figure must be accepted cautiously. Among 22 patients 14 made a good response to one dose of radioiodine and the remainder required a second or third dose. Two of the group remained mildly hyperthyroid and 4 developed myxedema. Reactions resembling roentgen ray ichthyosis occurred in 5.

Much remains to be learned about the ultimate effects of radioactive iodine. What it does to glomeruli and tubules in the presence of renal disease is unknown. Also unanswered is the question of whether it will pre-

11

Management of Hyperthyroidism

ACCORDING to the major pathology noted in the thyroid gland, hyperthyroidism falls into three categories. These are

- 1 Primary hyperthyroidism with or without exophthalmos
- 2 Adenomatous goiter with secondary hyperthyroidism (this includes toxic adenoma)
- 3 Thyroid cancer

In recent years several new discoveries have been made which when applied to thyroid disease have proved beneficial. Certain physiologic interpretations have added to the understanding of the ability of the gland to concentrate the iodide ion (often spoken of as iodine trapping). This trapping is not the same as the thyroid's physiochemical ability to elaborate iodine into thyroid hormone. This knowledge has been unfolded by observation of the pharmacologic reactions following the administration of goitrogenic drugs.

Thiocyanate prevents the concentration of iodide within the thyroid gland and the thiouracil compounds allow the absorption of iodide but inhibit the physiochemical transformation of iodine into the hormone. It is further believed that the antithyroid drugs actually prevent the formation of thyroxine.

With this newly gained physiochemical and pharmacologic knowledge a great change has taken place in the treatment of hyperthyroidism. Present day treatment of hyperthyroidism revolves around a choice of three methods. Two are medical and one is surgical. The medical methods are radioactive iodine and the thiouracil drugs; the surgical method is thyroidectomy.

Radioactive Iodine

The introduction of radioactive iodine therapy (1941) and the utilization of the thiouracil drugs (1943) have provided the medical therapeutic agents. The radioactive isotopes of iodine give off an intense radiation. The mode of action in suppressing hyperthyroidism can be explained physiologically. The thyroid cell needs iodine for hormone production and the hyperthyroid cell more than the normal cell is 'hungry' for iodine. Hence, these hyperthyroid cells readily grasp the iodine containing the radioactive isotope.

The isotope in organic iodine contains a large dose of radiation which is readily delivered to the overactive thyroid cells. If the dose is sufficient actual necrosis of the thyroid cell can result.

The normal thyroid gland picks up about 20 per cent of an ingested dose of radioiodine while the gland of the patient with hyperthyroidism will collect about 80 per cent. In myxedema little or none is collected by the gland. Both beta and gamma rays are emitted by radioactive iodine. The beta rays have a maximum range of only a few millimeters and radiation can thus be confined almost exclusively to the tissue holding the radioactive isotope. Collection of radioiodine by the thyroid usually occurs within a few hours. What is not absorbed is excreted readily by the kidney.

The principal isotopes used are I^{130} (with a half life of 12 hours) and I^{131} (with a half life of 8 days). Fifty per cent of the total radiation dose from I^{130} is delivered in the first 12 hours and 90 per cent within 36 hours. Determination of the amount required by a patient is partly guesswork since an estimation of the weight of the gland must be made in calculating dosage. Generally 5 mc to 25 mc will be effective. The calculated dosages in which internal radiation has been successful are from 500 to 2000 roentgens which agree with figures for external radiation. Generally used. Certain prerequisites for successful treatment have been advised. For example the patient should have received no previous iodine for at least one month; he should be available for close follow up; and he should be given routine iodination with Lugol's a few days after his original dose of radioiodine. Not all radiologists agree that Lugol's is necessary in every case. Contraindications to radioiodine include large goiters which require surgery to relieve pressure symptoms, pregnancy and kidney disease.

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Much remains to be learned about the ultimate effects of radioactive iodine. What it does to glomeruli and tubules in the presence of renal disease is unknown. Also unanswered is the question of whether it will pre-

dispose to neoplasia and whether or not radiations will damage surrounding tissues. Many years will pass before these questions can be answered.

ISOTOPE LABORATORY

Ambulatory _____ Isotope Laboratory Number _____
 Whl hair _____ Date _____
 Sx h _____

Name _____ Admission Number _____

Address _____

Age _____ Sex _____ Occupation _____ Div. _____

Clinical Diagnosis _____

Brief Resume of History _____

Examination or Treatment Desired

Radioactive Iodine 131 _____ Tracer Study _____ Therapy _____

Isotope Laboratory

1 Iodine 131 any form 1st 4 week _____ Yes _____ No _____
 2 Thyroid 131 any form in last week _____ Yes _____ No _____
 3 Thyroid 131 within 1st 2 week _____ Yes _____ No _____
 4 Antithyroid or 131 drug within last 2 weeks _____ Yes _____ No _____
 5 Leq d 131 br mtd with 1st 2 weeks _____ Yes _____ No _____
 6 Gall bladder 131 kid y study with dy within 1st 4 week _____ Yes _____ No _____
 7 Bone hography within 1st 2 month _____ Yes _____ No _____
 8 My 131 q phy at any time _____ Yes _____ No _____
 9 C rise or ACTH _____ Yes _____ No _____
 10 Prev Iodine plot study Y _____ N _____ Flinga _____
 11 Blood M 131 bolus Y _____ N _____ Flinga _____
 12 Blood Ch 131 131 es Y _____ N _____ Flinga _____

Radioactive Phosphorus 32 _____ Tracer Study _____ Therapy _____

Most re 1 _____ Wbe _____ Dth _____ B _____ E _____ My _____ S _____ Seg _____ L _____ M _____

Det _____ Rbe _____ Rb _____ Plat 131 _____

Other Isotope _____ Tracer Study _____ Therapy _____

M D

FIG 49 Copy of a standard chart from Isotope Laboratory. This chart is completed before the patient receives any isotope.

only because prolonged observation is imperative but also because the general use of these radioactive agents will remain limited for a time in certain areas.

Radioactive iodine is administered either in a single dose or in divided

ISOTOPE REPORT

HOSPITAL _____

P I _____

D I _____

Adm by _____

Adm by _____

Attending physician _____

Date _____

THYROID UPTAKE

| | TIME | 555 | 501 K | 701 | 5 | C.S.S. |
|------------|------|-----|-------|-----|---|--------|
| Background | | | | | | |

Patient

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| Ant | | | | |
| R.S.d | | | | |
| L.S.d | | | | |
| P.T. | | | | |

T.T.T.

A. ng

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| R. and L. | | | | | | |
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(2)

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| Standard | | | | | | |
|----------|--|--|--|--|--|--|

(3)

3-2=Cor at Standard

 (4)

$$p \pm hr \left[\frac{(1)}{(7)} \right] \sim 100 \% \text{ } \underline{\hspace{2cm}} \%$$

Dih. A

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ISOTOPE LABORATORY

FIG 50 This chart is filled out after the patient has received a radioactive substance

does according to the radiologist's preference for technique. Relief from thyrotoxicosis is complete if a sufficient dose of radioactive iodine is given. Surprisingly, no great damage to the parathyroid glands has been reported following the administration of radioactive iodine.

The major disadvantage of radioactive iodine is the possibility of delayed carcinoma formation. It should be given, therefore, only to patients in whom this question may not arise. It may be given to other individuals in whom this disadvantage is outweighed by greater disadvantages which would result if another form of therapy was chosen. It is the therapy of choice in the geriatric patient who is a poor operative risk or in an individual who has had recurrence following one or two thyroidectomies.

Radioactive iodine is not the treatment of choice in adenomatous goiter with hyperthyroidism for the following reasons:

1. There is a high incidence of carcinoma in adenomatous goiter.
2. Doses would have to be high and would have to be repeated at intervals.
3. The size of the goiter may not recede. If it does, nodules may persist which necessitate surgical removal.

Madigan and King of Australia report the study of a research group. The group including physician, radiotherapist, physicist, a pathologist and a biochemist undertook to investigate the following:

1. The value of physical indices concerning uptake and excretion of tracer doses of radioactive iodine (I^{131}) as an indication of thyroid function.
2. The value of protein bound iodine as an index of thyroid function.
3. Comparison of the value of physical indices, protein bound iodine and basal metabolic rate estimations in the same group of patients compared to clinical assessment.
4. Comparison of various physical indices to determine the most useful.
5. Clinical trial of I^{131} as a therapeutic agent in hyperthyroidism and carcinoma of the thyroid.
6. Investigation of superior mediastinal tumors with tracer doses of I^{131} to detect thyroid tissue if present.
7. Establishment of a method of radioautography.

The extensive paper and two others to be published later report the results of the joint project carried out at the Royal Melbourne Hospital. The first part of this paper is concerned with the clinical assessment of the 140 tracer tests carried out on 114 patients. 72 of the tests were made on 66 subjects with normal thyroid function, 65 on 45 patients with thyrotoxic hyperthyroid function, and 3 tests on 3 patients with hypothyroid

function (myxedema). Clinical assessment gave correct classification for 128 of 140 tracer tests. Physical indices gave correct classification for 113 of the total 140 performed. Protein bound iodine estimation gave correct classification for 111 tests of a total 131 performed. The basal metabolic rate gave correct classification for 40 tests and inconclusive or incorrect results for 36 of the total of 76 performed. The analysis of 23 patients with hyperthyroidism who were treated with I^{131} revealed that 3 have since died of cardiac failure existent at the time of I^{131} therapy and of hypertensive or rheumatic causes in addition to a thyrotoxic element. Two of the 3 patients had their thyrotoxicosis controlled by a single dose of I^{131} and the other died two months after a single dose with only partial control. Twenty patients are still alive. Ten of these had their hyperthyroidism controlled and have been under observation for 6 months to 3 years. Of the remaining 10 patients 4 improved but were only partly controlled. The period of observation since the last dose has been between 2 and 11 months. Five patients have been in a nontoxic state since their last therapy dose was given 3 to 5 months ago: insufficient time has elapsed to determine whether their condition will be controlled. Because a superior mediastinal tumor may be a retrosternal thyroid mass 10 patients with mediastinal masses were studied by tracer tests with radioactive iodine. Notwithstanding certain difficulties such as the close proximity of the superior mediastinum to the thyroid there was sufficient uptake in the mediastinal mass in 6 of the 10 patients tested to indicate the thyroid tissue content. This conclusion was later verified at operation in each of these 6 patients. The therapeutic use of radioactive iodine in malignant lesions of the thyroid was limited. Only 5 of 17 patients with suspected thyroid carcinoma were given therapeutic doses of radioactive iodine the others being regarded as not suitable for this treatment.^{3,7}

At this stage of the discussion I should like to record the story of a patient who was among the first individuals to receive this therapeutic form of iodine.

Case History of a Patient Treated with Radioactive Iodine. In March 1947 Mrs. M. S., a 41-year-old housewife, was first seen by the author as a hospitalized patient. At that time he was transferred from the gynecological service to surgery because of symptoms indicative of hyperthyroidism. She was admitted to the hospital primarily for an elective vaginoplasty. Her hyperthyroid history was of 2 years' duration.

The classic symptomatology was present including an enlarged thyroid gland and exophthalmos. At the time of admission she weighed 158 lbs and her B.M.R. was +64. Subsequently it was +37, +35, and +15. No antithyroid drug was employed. Electrocardiogram demonstrated tachycardia consistent with hyperthyroidism; no organic cardiac disturbance was recorded. I roperative x-ray studies failed to reveal any evidence of metastases.

A significant fact in the patient history was a left-sided kidney operation performed in 1939. Intravenous pyelograms taken in 1947 demonstrated that a partial left nephrec-

tomy had been performed. The remaining left renal tissue and the right kidney were normal (Urinalysis was negative). The reason for the partial left nephrectomy could not be determined.

On March 25, 1947 a total thyroidectomy was performed. At the time of operation malignancy was suspected in the gross specimen. The histological report was adenocarcinoma.

Postoperatively the patient was given radiation therapy to the neck. A total of 416 R was given. Following radiation she was given radioactive iodine I^{131} (8 day half life). The radioactive iodine was obtained from the Clinton Laboratories, Oak Ridge, Tenn.



FIG 51 This photograph was taken several months after the administration of radioactive iodine. There is noted a marked gain in weight, myxedema, and a persistence of exophthalmia (more prominent on the left side).

Twenty-four cc was administered orally. Each cubic centimeter contained 3.1649 mc of the isotope. A total of 76 mc was given to the patient. This was a total of 10,105 mc/hrs (76×133). Following this procedure the Geiger counter demonstrated a generalized disturbance.

On June 6, 1947 her BMR rose to +77, blood cholesterol was 160 mg.

A tracer dose of 5 mc of radioactive iodine was given. X-rays of the skeletal system did not reveal any metastases. The patient was readmitted to the hospital from August 25, 1947 to September 11, 1947 for complete study. No evidence of metastases was found.

The patient left the hospital refusing further treatment and would not allow any doctor to visit her. Finally a photographer was sent to her home. The result is produced herewith.

At the time the photograph was taken she had gained weight and evidence of myxedema was present.

The patient was not seen again until September 29, 1919, at which time she was treated in the clinic. Her weight was 190½ pounds. She had marked myxedema for which thyroid extract was prescribed. On October 29, 1919, her weight was 208½ pounds. A notation was made that she was five months pregnant. Her weight increased by November 17 to 210½ pounds and by December 9 to 213 pounds. At this time she was taking 3 grains of thyroid extract. X-ray studies failed to demonstrate any recurrence of the thyroid lesion.

She was not seen again. A follow-up letter was sent to her home. Her daughter replied that the patient died on January 26, 1920, following the birth of a normal son.

A letter was sent to the hospital where the patient expired. No autopsy was performed. Death was attributed to renal failure secondary to toxemia of pregnancy.

Summary. This patient with carcinoma of the thyroid gland was treated by surgical removal of the gland, radiation therapy, and radioactive iodine. Following this therapeutic regimen she developed myxedema which necessitated the administration of thyroid extract. The patient became pregnant and died following the birth of a normal infant. Death was attributed to toxemia of pregnancy. No autopsy was obtained. In the absence of definite anatomical findings revealed at autopsy, no positive conclusions can be reached. However, it is known that radioactive iodine is excreted by the kidney. This patient's previous kidney operation plus the clinical evidence of renal failure with a toxemia of pregnancy strongly suggests that kidney damage was present at the time of death.

This report, although incomplete because of the failure to obtain an autopsy, nevertheless is of value as one of the first medical histories of a patient who was among the early recipients of radioactive iodine.

Treatment of Thyrotoxicosis with Potassium Perchlorate

An interesting report has been published in the English literature on the use of potassium perchlorate in hyperthyroidism. Potassium perchlorate inhibits the uptake of radioactive iodine by the thyroid of animals as well as of man. It has been used in the treatment of patients with thyrotoxicosis. Morgan and Trotter tried potassium perchlorate in the hope that it might prove effective in controlling thyrotoxicosis without exposing the patient to the risk of the toxic side effects sometimes seen with the thiouracil drugs.¹⁰¹ Perchlorate acts only on the iodide concentrating mechanism of the thyroid. Thiouracil on the other hand leaves this mechanism unaffected but prevents the oxidation of iodide and its subsequent incorporation into protein molecules to form thyroglobulin. Thiouracil is therefore effective whatever the concentration of iodide in the blood, but perchlorate would become ineffective with blood iodide levels

tomy had been performed. The remaining left renal tissue and the right kidney were normal (Urinalysis was negative). The reason for the partial left nephrectomy could not be determined.

On March 25, 1917, a total thyroidectomy was performed. At the time of operation, malignancy was suspected in the gross specimen. The histological report was adenocarcinoma.

Postoperatively, the patient was given radiation therapy to the neck. A total of 41.6 R was given. Following radiation, she was given radioactive iodine I^{131} (8 day half life). This radioactive iodine was obtained from the Clinton Laboratories, Oak Ridge, Tenn.



FIG. 51. This photograph was taken several months after the administration of radioactive iodine. There is noted a marked gain in weight, myxedema, and a persistence of exophthalmia (more prominent on the left side).

Twenty-four cc was administered orally. Each cubic centimeter contained 3,164.9 mc of the isotope. A total of 76 mc was given to the patient. This was a total of 10,108 mc/hrs (76×133). Following this procedure, the Geiger counter demonstrated a generalized disturbance.

On June 6, 1947, her BMR rose to +77; blood cholesterol was 160 mg.

A tracer dose of 5 mc of radioactive iodine was given. X-rays of the skeletal system did not reveal any metastases. The patient was readmitted to the hospital from August 25, 1947, to September 2, 1947, for complete studies. No evidence of metastases was found.

The patient left the hospital, refused further treatment, and would not allow any doctor to visit her. Finally, a photographer was sent to her home. The result is produced herewith.

At the time the photograph was taken he had gained weight and evidence of myxedema was present.

The patient was not seen again until September 2, 1949 at which time he was treated in the clinic. Her weight was 199½ pound. She had marked myxedema for which thyroid extract was prescribed. On October 29, 1949 her weight was 205½ pound. A notation was made that he was five months pregnant. Her weight increased by November 17 to 210½ pound and by December 9 to 213 pound. At this time he was taking 3 grains of thyroid extract. X-ray studies failed to demonstrate any recurrence of the thyroid lesion.

She was not seen again. A follow-up letter was sent to her home. Her daughter replied that the patient died on January 26, 1950 following the birth of a normal son.

A letter was sent to the hospital where the patient expired. No autopsy was performed. Death was attributed to renal failure secondary to toxemia of pregnancy.

Summary. This patient with carcinoma of the thyroid gland was treated by surgical removal of the gland, radiation therapy and radioactive iodine. Following this therapeutic regimen he developed myxedema which necessitated the administration of thyroid extract. The patient became pregnant and died following the birth of a normal infant. Death was attributed to toxemia of pregnancy. No autopsy was obtained. In the absence of definite anatomical findings revealed at autopsy, no positive conclusion can be reached. However it is known that radioactive iodine is excreted by the kidney. This patient's previous kidney operation plus the clinical evidence of renal failure with a toxemia of pregnancy strongly suggests that kidney damage was present at the time of death.

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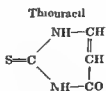
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sufficiently high to raise the concentration within the thyroid to the level normally attained by the gland's iodide concentrating mechanism. A patient in whom thyrotoxicosis is controlled by perchlorate would be liable to relapse if his blood iodide level were suddenly raised for example by the administration of an iodide containing cough medicine. This is a theoretical difficulty, but so far Morgans and Trotter have not observed it. It might also be expected that if a thyrotoxic patient is prepared for operation with perchlorate similar difficulties would arise when iodide is added during the final stages to reduce the vascularity of the goiter. Potassium perchlorate was made up in either 50 or 200 mg tablets. The *dosage* were administered either once or twice daily. The patients were usually seen at monthly intervals. In a *dosage* of 400 mg daily potassium perchlorate was effective in controlling thyrotoxicosis in most patients. The rate of response appeared to be somewhat slower than with methylthiouracil, and in one of 25 previously untreated patients control was not complete. When patients receiving maintenance doses of methylthiouracil were given potassium perchlorate instead control of the thyrotoxicosis was maintained in all but 2 of 64. The average *dosage* necessary was 2 to 4 times that of methylthiouracil. No toxic effects were seen in 108 patients treated with potassium perchlorate except signs of gastric irritation in 2 patients with a history of dyspepsia.¹⁶¹

The Antithyroid Drugs

Within our own lifetime, we have seen the remarkable results achieved in the treatment of thyrotoxicosis by means of thiourea, thiouracil, trimethyl and other similar sulfur compounds. These drugs have a more pronounced and striking effect in abating the toxic symptoms than any other medication known to mankind. Their mode of action provides a new and fascinating study in the field of the physiological chemistry of the endocrine system.



Astwood's introduction of the thiouracil compounds showed that the drugs block the elaboration of iodine into the hormone.^{162, 163, 164} With this blockage there is an increase in the activity of the antithyroid on the thyroid cells causing hyperplasia. The anatomic result of the drugs on

the thyroid gland is the direct opposite of the effect produced by iodine. Iodine when given with the thiouracil compounds, is able to produce involution of the gland in spite of the thiouracil. It is possible to control the thyroid function of almost any degree of toxicity by varying the dosage of the antithyroid drugs. It is a common practice to administer large doses initially and then to reduce the dosage when a normal metabolic rate has been reached.

The judicious use of the thiouracil drugs results in a satisfactory control of hyperthyroidism. Usually, there is a very high recurrence of toxic symptoms following the withdrawal of these drugs. Therefore the drug must be administered until the metabolism is normal for 6 to 16 months in order to assure a cure. Even after this long period of treatment 50 per cent have a recurrence. Thus another form of therapy may be necessary to produce a cure even after prolonged use of the antithyroid drug.

In the beginning thiouracil and thiouracil were the only drugs available. Thiouracil was bitter to the taste so that thiouracil was preferred by the patient. This drug however was quite toxic and constant observation was imperative. Other new drugs which had less toxic reactions were developed. These were methylthiouracil, trimethylmercaptoimidazole, tapazole and propylthiouracil. The latter drug is preferred because of its low toxicity. More recently two iodinated thiouracil compounds have been manufactured. Use of the iodinated drugs has not been extensive so that an exact evaluation of them cannot be made at this time.

The possibility that thiouracil compounds might have a carcinogenic tendency is a warning against their use in certain individuals. For this reason it is not the treatment of choice in simple thyroid adenoma where the incidence of a hidden malignancy may be as high as 8 per cent. It should not be administered over a long period of time in adenomatous goiters for the same reason. In any patient who has received the antithyroid drugs over a period of years the possibility of malignant changes should be remembered. Any unusual increase in size of a goiter under this form of therapy especially if this increase is asymmetrical should be an indication for surgical intervention.

Attention must be called to the fact that the antithyroid drugs may result in some disturbance to sensory nerves. The toxic effects are loss of smell and taste following the prolonged use of propylthiouracil and methylthiouracil. These neurotoxic manifestations should be remembered when the thiouracil drugs are employed. In the cases reported to date these sensory disturbances were not permanent. The discontinuation of the drug and high doses of vitamin B complex usually ameliorates the sensory toxic symptoms.

Effects of the Antibiotics on the Thyroid Gland

At any symposium on the thyroid gland, the question almost always raised is 'What are the negative or positive effects of the antibiotics on the thyroid gland?' Recently Clesnick, Harris and Jones in an issue of *Science* (119-128 1954) reported that penicillin as well as aureomycin produced a goitrogenic and antithyroid effect in experimental animals. They base their conclusion upon the increase in the weight of the thyroid gland and the decreased uptake of I^{131} in the experimental animals. Inasmuch as the antibiotics are so widely used in the treatment of human diseases it is well to have a definite answer as to whether penicillin and/or aureomycin can alter the activity of the thyroid gland. Experimental work of recent origin strongly indicates that penicillin and aureomycin are not goitrogenic and do not decrease the uptake of I^{131} in experimental animals or by inference in human beings. As a general statement therefore it may be stated that there is a lack of sufficient evidence to warrant the belief that there is any direct action by the antibiotics on the thyroid gland.^{213, 214}

The Antithyroid Action of Para-aminosalicylic Acid

It has been known for years that many aminophenol compounds have a goitrogenic action. Astwood showed in 1943 that *p*-aminobenzoic acid inhibited thyroid gland function in rats. The closely related substance *p*-aminosalicylic acid and its sodium salt have been extensively used in the treatment of tuberculosis in England. Macgregor and Somner²¹⁵ cite observations by others that make it apparent that *p*-aminosalicylic acid can in some circumstances when used in normal dosage for the treatment of tuberculosis in man produce clinical hypothyroidism. They tried to assess the true incidence of goiter and hypothyroidism in a fairly large group of patients being treated with this drug. The thyroid function of the patient was evaluated with radioactive iodine. They found an incidence of goiter with hypothyroidism developing in 23 per cent of the patients under observation. Studies with the isotope revealed that all patients receiving *p*-aminosalicylic acid showed changes in thyroid function. Although the goitrous and hypothyroid state induced by this drug is usually reversible on the withdrawal of the drug, the authors feel that thyroxine should be given to all patients in whom a goiter is noted or to whom *p*-aminosalicylic acid is given for more than six months.

Surgical Treatment

Mortality and morbidity following thyroid procedures are rapidly fading away. These results are due in great measure to the excellent preoperative

regimens employing the antithyroid drugs. Today, the thyroid patient is operated upon just like any normal person undergoing surgery. No stealing of the thyroid under avertin and the like is now necessary. Among the advantages of surgical intervention are the following:

- 1 The pathology is definitely established
- 2 The presence of cancer is detected and radical surgery can be performed immediately
- 3 Prolonged medical therapy is eliminated
- 4 The goiter is removed by surgery. Antithyroid drugs may even increase the size of the gland. Radioactive iodine may diminish the size of the goiter but the hidden possibility of malignancy at some future date remains.
- 5 Operative therapy produces no carcinogenic activity.

Moreover, thyroidectomy, for many years has been a widely and highly effective method in the control of exophthalmic goiter. After proper preparation it can be carried out with a minimal surgical mortality except in the unusual and very complicated case. Thyroidectomy is followed by postoperative myxedema in less than 3 per cent and by recurrent or persistent hyperthyroidism in a little more than 5 per cent of patients subjected to surgery. The incidence of parathyroid insufficiency or injury to the recurrent laryngeal nerve, resulting in permanent paralysis of the vocal cords is very low in the hands of the competent thyroid surgeon. In the majority of patients treated surgically the basal metabolic rate decreases to normal or to near normal levels within three weeks after operation. Therefore surgery must be considered as a rapid and highly effective method of controlling hyperthyroidism.

Practical Aspects of Thyroidectomy

Certain aspects of thyroidectomy which have proved beneficial are presented here in summary.

Exposure. The usual collar-like incision of the skin is made about 2 to 4 cm. above the sternoclavicular junction. A low incision is made in order to facilitate exposure of the lower thyroid arcs, wherein vital structures are found. In addition the low incision eliminates dead space where fluid may accumulate since the area close to the clavicle is more fixed. It must be remembered that thyroid incisions are made while the patient's head is extended. Following operation with the head in a normal position the incision may descend as much as 2 to 3 cm. The skin flap is dissected up to the thyroid cartilage in order to allow exposure of the thyroid poles.

Division of Prethyroid Muscles. Whether to divide the prethyroid muscles or not is a matter for the individual surgeon to decide. Any method

to which the surgeon has become accustomed is the best in his hand. The author's personal preference is to divide the muscles high at the junction of the upper and middle thirds in order to avoid the ansa hypoglossi nerve and the superior laryngeal nerve. This high division does not interfere with the healing of the low skin incision, nor does the division of these muscles increase serum collections. The excellent exposure of the thyroid gland, when the muscles are divided far outweighs any objection offered against this procedure.

So called Thyroid Capsule. At the operating table, the surgeon does not find a true thyroid capsule which will enable him to encircle the gland. It is true, however, that there are certain lines of cleavage which form a sheath with attachments to the thyroid gland. The so called capsule is a reflexion of a plane of the deep cervical fascia. A layer of thin areolar tissue is found on the inner surface of the sternothyroid muscle. This layer is associated with the pretracheal fascia which in turn continues as the anterior portion of the sheath of the thyroid gland. This anatomic formation permits the identification of cleavage planes, which when followed mobilize the thyroid gland and gives rise to the faulty interpretation that a separate thyroid capsule completely encircles the gland. If one will recall the fascial planes of the neck, it will be evident that no true thyroid capsule exists.

These fascial planes may be grouped as follows:

First plane Subcutaneous fascia and platysma muscle

Second plane Fascia of sternocleidomastoid and trapezius muscles

Third plane Fascia of the sternohyoid muscle (*Fig. B*). The second and third fascial planes blend posteriorly.)

Fourth plane Fascia of the sternothyroid muscle and the fascia of the carotid sheath. This fascial plane blends with the pretracheal fascia and the layer of fascia (so called capsule) encompassing the thyroid gland.

Fifth plane This is a posterior layer called the prevertebral or retrovisceral fascia.

The fifth plane does not concern the thyroid surgeon but is important to the thoracic surgeon who must deal with ingested foreign bodies.

Thyroid Vessels. An axiom of major significance to the thyroid surgeon is never to clamp blindly in a pool of blood. There are so many vital structures in a small circumscribed area that the clamp may crush what is not intended to be clamped. For this reason it is preferable to ligate the major thyroid vessels first then any technique which pleases the operator may be followed according to his individual plan. The major vessels in question are the superior and inferior thyroid vessels, the

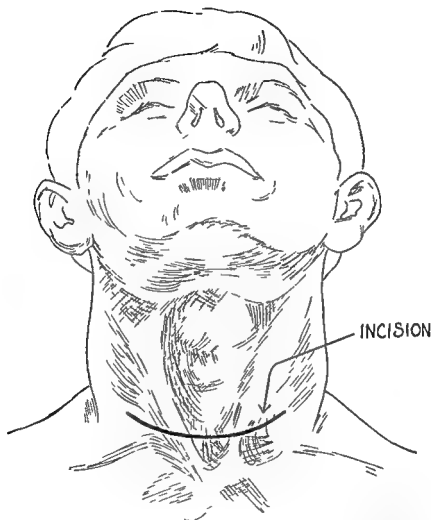


FIG 52 This drawing illustrates the usual collar like incision which is performed as an initial step in a classic thyroidectomy. It is noted that the chin is extended maximally, the thorax is forward and the neck assumes a goiter position. This anatomic position is obtained by placing the patient on the operating table in a concave position with the head markedly elevated and the feet raised to a comparable height with the thorax. In this position the surgeon then makes the skin, placing the incision a little higher than the location he desires it to be ultimately (because the incision will descend from 2.5 cm to 4 cm after healing depending upon the size of the original underlying goiter). One should remember that a thyroid incision is made with the eye and not with a measuring rule.

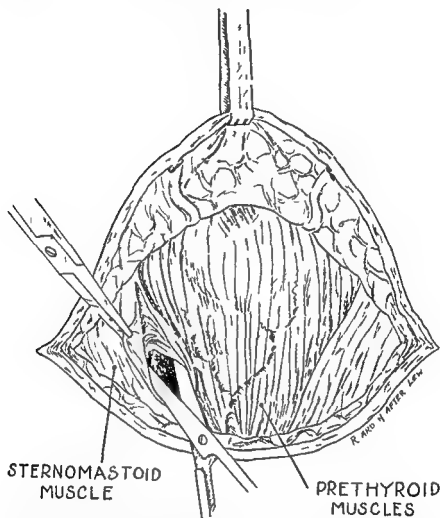
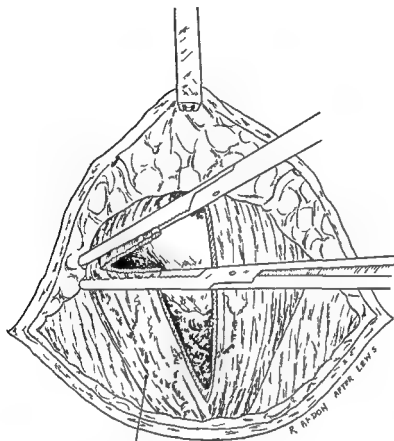


FIG. 53 An exemplification of the height to which the skin flap is dissected. This dissection is carried superiorly to the thyroid cartilage. On occasion the skin flap will include the platysma muscle when it is visible. In patients with a well developed neck the skin flap is raised to above the thyroid notch (inferior border of the thyroid cartilage). Elevation of the skin flap is necessary in order to adequately expose the thyroid gland especially the superior thyroid vessels at the upper pole of the gland. This diagram depicts the separation of the sternocleidomastoid muscle from the prethyroid muscles. The incision liberates the sternocleidomastoid muscle enabling the assistant to retract it laterally for a more satisfactory division of the prethyroid muscles on that side. (Thyroid cartilage is represented by shaded area in midline below thyroid double hook.)



PRETHYROID MUSCLE

FIG 54 A wider exposure is possible with retraction of the sternocleidomastoid muscle. Clamps are then placed across the prethyroid muscles at the junction of the middle and upper thirds of these muscles. Division of the muscles at this level protects the nerves going to the prethyroid muscles and an excellent exposure of the gland results. In addition a division of the muscles at this location can be repaired with a resulting suture line that is high under the skin flap without interfering with the closure of the skin and at the same time eliminating the possibility of adherence of the skin to the underlying muscle.

middle thyroid vein and the main vessels. There is no middle thyroid artery. Double ligation of the arteries results in a diminution of blood supply to the gland so that it may be dissected with a less bloody field. The middle thyroid vein should be ligated and divided as soon as it is

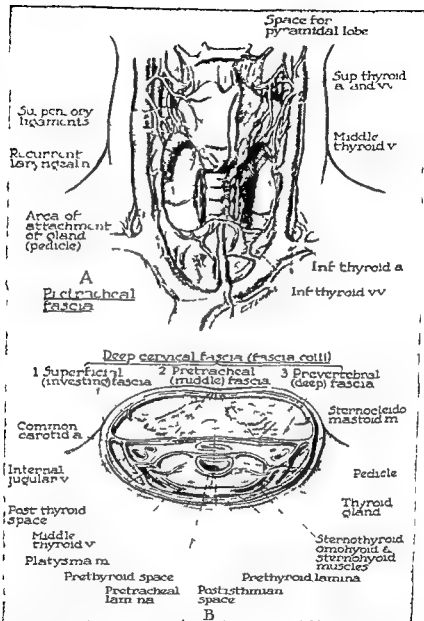


FIG 50 A surgical anatomic exposure of the neck to illustrate the fascial layers of the neck *

A The suspensory ligaments of the thyroid gland are shown passing from the inner margins of the gland to the cartilaginous framework. The blood vessels and the recurrent laryngeal nerve as related to the pretracheal fascia are demonstrated

B The deep cervical fascia (fascia colli) is pictured in cross section. This fascia is conceived as consisting of three layers: superficial or investing layer, middle or pretracheal layer, and the deep or prevertebral layer. The anterior and posterior thyroid spaces (also termed the pre- and post-thyroid spaces) are seen in relation to the middle thyroid vein.

identified because when damaged, it bleeds briskly like an artery. The same is true of the thyroid ima vessels.

The superior thyroid artery is the first branch of the external carotid artery. The superior thyroid vessels are located between the pretracheal and prethyroid laminae and are found a little above the thyroid cartilage. The inferior thyroid artery is larger and carries more blood than the superior vessel. It arises via the thyrocervical trunk from the subclavian artery, emerges from behind the carotid sheath, penetrates the posterior aspect of the pretracheal fascia and passes medially to the gland where it may divide into two or more branches. The inferior thyroid veins and ima vessels are situated inferiorly between the prethyroid and pretracheal fascial laminae. Knowledge of their location makes possible their rapid identification and immediate ligation.

The Laryngeal Nerves. Possible injury to the laryngeal nerve is always thought of by the thyroid surgeon. Both laryngeal nerves, superior and inferior, supply the sensory and the motor innervation of the larynx.

The superior laryngeal nerve arises from the vagus (see Figs. 62 to 66). Both motor and sensory, this nerve divides into two branches, one external and one internal. The external branch (motor) supplies the cricothyroid muscle and serves as the tenor of the vocal cords. The internal branch (sensory) innervates the mucosa of the larynx, epiglottis and part of the pharynx. Section of the superior laryngeal nerve causes a loss of sensation in the laryngeal mucosa and paralysis or relaxation of the cricothyroid muscles, resulting in a lowering of pitch and a diminution in the clearness of the voice. The loss of sensation causes an inability to perceive the entrance of foreign bodies into the larynx. The superior laryngeal nerve can be protected if the superior pole is ligated as the gland is retracted downward and if the pole is ligated even with the point of entrance of the blood vessels into the pole.

The inferior laryngeal (recurrent laryngeal) arises at the level of the subclavian artery on the right side, goes around the artery and ascends toward the thyroid gland. The left recurrent arises from the vagus in front of the aortic arch and ascends toward the left lobe of the thyroid. Both right and left recurrent nerves may course outside or inside the inferior thyroid artery or between its branches.

The inferior laryngeal nerve supplies the motor branches to the intrinsic muscles of the larynx. It enters the larynx behind the inferior cornu of the thyroid cartilage. It is known that the inferior laryngeal nerve is composed of two bundles of fibers, one for the adductor and the other for the abductor muscles. Injury to one inferior laryngeal nerve affects the adductors but respiration continues. The loss of the voice may be temporary.

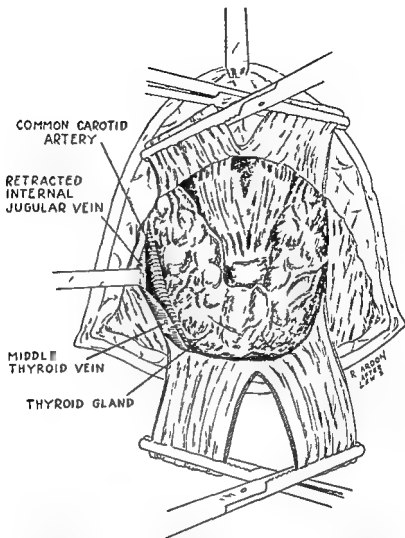


FIG. 56 The next step in performing an orderly thyroidectomy is to ligate and then divide the middle thyroid vein. This is done easily if the assistant retracts the internal jugular vein laterally by means of a blunt retractor. After the middle thyroid vein is divided, the underlying common carotid artery is brought into view. The assistant then replaces his retractor so that the common carotid artery is now pulled gently in a lateral direction. This facilitates exposure of the superior thyroid artery which is doubly ligated in continuity and then divided. The superior pole of the thyroid gland is thus liberated. By gentle retraction inferiorly, the bare area of the trachea is exposed on the posteromedial aspect of the thyroid lobe. This is a bloodless area and permits a prompt liberation of the upper third of the thyroid lobe.

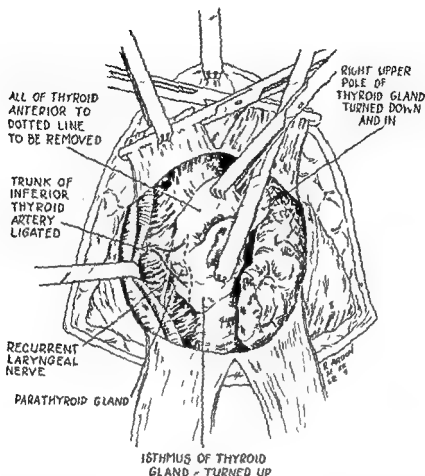


FIG. 57 This diagram depicts the right thyroid lobe retracted inferiorly and medially after the superior pole has been ligated and divided. The bare area of the trachea lies immediately beneath the upper thyroid double hook clamp. The retraction of the lobe in this position allows a clear identification of the inferior thyroid artery which is shown ligated in this drawing. The dotted line along the lateral surface of the thyroid lobe indicates the site where the incision will be made into the gland tissue; all the parenchyma above this line will be removed in toto. The close proximity of the parathyroid gland to the inferior thyroid artery is demonstrated.

since the unimpaired vocal cord may pass over the middle line and contact the paralyzed one. Phonation then occurs.

Unilateral injury to the abductor fibers results in a fixed midline paralysis of the vocal cord. Respiration continues as well as phonation be-

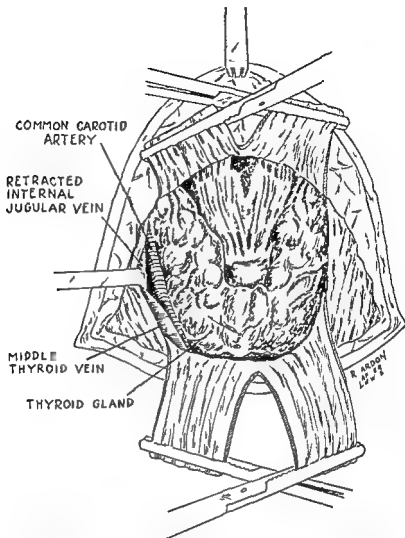


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cause the impaired cord allows ample breathing space and brings both cords into close approximation

If both nerves are injured bilateral abductor paralysis results. The vocal cords are in permanent adduction. The patient can speak but can not breathe. Tracheotomy then must be performed.

In order to avoid injury to the recurrent nerves some surgeons have advocated a routine identification of the nerve. In such cases the inferior thyroid artery is the guide to finding the nerve. Routine nerve identification is not always necessary especially for the noninitiated in this procedure. Other precautions must be taken however.

Most injuries to the recurrent nerves occur at the lower pole of the thyroid gland and at the point of its entrance to the larynx through the inferior constrictor pharyngeal muscle. The surgeon therefore must avoid undue trauma in these areas and he should expose the posterolateral surface of the lobe by retracting it forward. Thereafter constant visualization of the operative site with a knowledge of the anatomic pathway (unless the nerve travels within the gland as an anomaly) will prevent nerve injury.

A preoperative laryngoscopy will identify the existence of any paralysis

B Another approach of the inferior thyroid artery in which the vessel forms an upward arch and then descends behind the thyroid lobe to enter the gland. This arch may be so high in some patients as to reach the level of the superior thyroid artery.

C When the inferior thyroid artery passes from below upward at an acute angle as shown here it is most difficult to demonstrate at the operating table. The surgeon may be lulled into a false sense of security in not being able to demonstrate the artery and he may believe that it is absent. It is rarely absent and can be demonstrated by lifting the lower pole of the lobe out of its resting position. As an aid in visualization and identification a blunt retractor is placed on the common carotid artery and it is retracted laterally. The retractor should be placed lower than the point of exit of the artery.

D This illustration exemplifies a common anatomic finding in which the artery bifurcates before entering the gland at a distance quite away from the margin of the lobe so that it may be erroneously thought that there are two arteries.

E Another illustration of a preglandular bifurcation in which the artery divides behind the common carotid artery. This type of vessel is very deceiving in that one branch only may be ligated and the other missed completely. The result is that bleeding becomes brisk when the gland is incised. It is well to remember (when bleeding is severe and difficult to control) that a second branch of the inferior thyroid artery may be the cause. Location of this vessel and its proper ligation will result in a less bloody operative site.

F Rarely does one encounter the absence of an inferior thyroid artery. It does occasionally occur however and in its place one can find a thyroidea ima artery. This artery enters the lobe in the lower pole in a location corresponding to the point of entrance of the superior thyroid artery so that if an imaginary line is drawn from one to the other there would be an almost immediate and accurate connection between them.

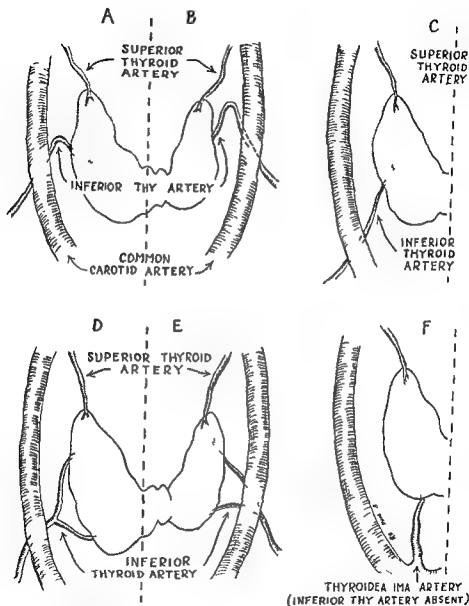


FIG 88 These drawings exemplify the various positions assumed by the vascular structures of the thyroid gland. The important arterial structures are the superior and inferior thyroid arteries and the major venous structures are the superior middle and inferior thyroid veins plus the thyroidea ima vein.

A The superior thyroid artery is almost always consistent in its entrance to the thyroid lobe at its superior pole. The inferior thyroid artery varies much more than the superior one. This diagram shows the most common pathway of the inferior thyroid artery as it enters the gland directly.

cau = the impaired cord allows ample breathing space and brings both cords into close approximation

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of the nerve due to a displacing pressure resulting from retrotornal or adenomatous projections of the thyroid gland. When there is a preoperative

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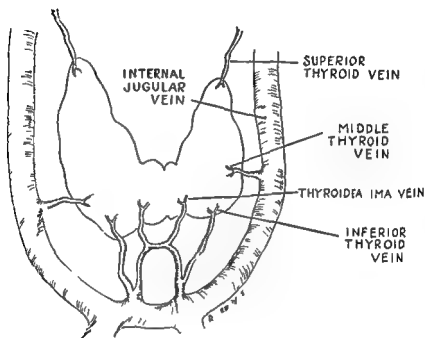


FIG 58 G A diagrammatic representation of the venous return of the thyroid gland. Generally speaking the veins in the superior poles correspond to the arteries on either side. The middle thyroid veins are usually found alone and the inferior thyroid vein is more consistent in location than the inferior thyroid artery. The vein is usually found leaving the inferior pole of the lobe on either side. More medial than the inferior thyroid vein is the thyroidea ima vein which is easily torn if the gland is retracted quickly. In order to accurately liberate the thyroid gland from its bed and perform a neat dissection one must ligate and divide the venous channel. When ligation is performed the ligatures should not be placed too close to the internal jugular vein because the ligature can slip easily when the assistant attempts to sponge the operative field. A simple sliding motion along the course of the internal jugular vein is often sufficient to disrupt what seems to be a securely tied ligature.

paralysis of the recurrent laryngeal nerve the surgeon knows in advance that the operative procedure can not produce this damage. However, it is to be remembered that the danger of nerve injury is increased greatly when a second operation is performed on a small adherent toxic thyroid gland. Thought must also be given to the fact that a partial paralysis or paresis

in the decibel measurement of the voice may last for 6 to 8 weeks. Under this circumstance there is no need for tracheotomy since the patient has no respiratory distress. It is therefore not in any way similar to injuring the superior laryngeal nerves bilaterally.

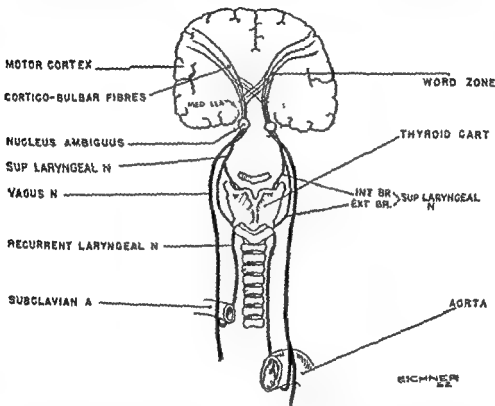


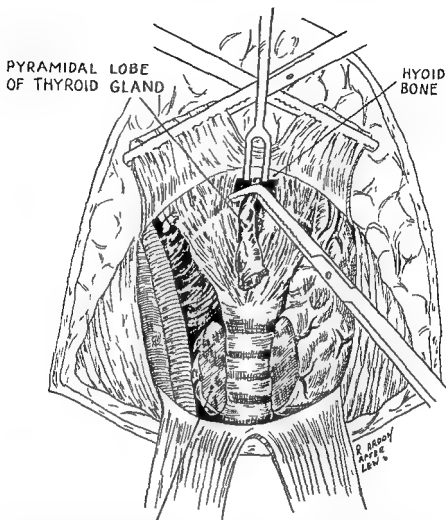
FIG 61 Concept of the origin and course of the recurrent laryngeal nerve (Ross D E Paralysis of recurrent laryngeal nerve *Am J Surg* June 1953)

Simon's law postulates the consecutive triad of changes in nerve injury

- 1 Adduction loss occurs leaving the vocal cord in the adducted position
- 2 Tension loss relaxes the cord further
- 3 Adduction loss in the final stage shows the vocal cord in the partially abducted midcadaveric position

Injury to the recurrent laryngeal nerve may result in the following alteration in vocal cord function

- 1 Respiration is obstructed causing stridor
- 2 Phonation is affected resulting in speech defects



STUMP OF THYROID GLAND TO REMAIN

FIG. 60 A pyramidal lobe may be present in about 40 to 50 per cent of patients with hyperthyroidism. It should be removed especially in patients with exophthalmic goiter because otherwise it may be the cause for a persistence of hyperthyroid symptoms. Moreover it may enlarge following thyroidectomy, resulting in a visible mass in the center of the neck. This diagram shows that the pyramidal lobe often extends high up in the neck, often as far as the hyoid bone. The proper placing of a retractor at the point where the prethyroid muscles separate will enable the surgeon to remove the pyramidal lobe in toto. This illustration shows the ligation of the superior thyroid vessels. These vessels should be checked before closing the neck because these ligatures may slip easily when the patient commences to react from the anesthesia. Slight coughing or the exertion concomitant with nausea and/or vomiting may be sufficient to produce a hemorrhage. The thyroid remnants are seen before they are sutured to the trachea.

3. Expulsion of foreign bodies is affected producing an interference in the cough mechanism.

Avoiding Removal of Parathyroids Accidental removal of the parathyroid glands results in tetany. The safest method of preserving these structures is not to include them in the portion of thyroid being resected. These structures are usually found in the posterolateral surfaces of the thyroid gland.

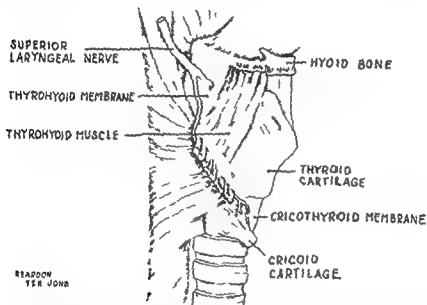


FIG. 64 Lateral view illustrating the position and course of the superior laryngeal nerve and its relationship to the prethyroid muscles and the thyroid muscle. When the sternohyoid and the sternothyroid muscles are divided the underlying nerve may be injured.

The parathyroid gland is kidney bean in shape mahogany brown in color and has molded edges. It is concave on the inside and convex on the outside. The parathyroids change color becoming darker upon exposure to the air because of embarrassed circulation.

Before discarding any thyroid tissue from the operating table the surgeon should examine all specimens to ascertain the presence of any accidentally removed parathyroid. These glands are commonly found along the main vascular channels.

If a parathyroid has been removed unintentionally it should be transplanted. It is necessary to return the gland to surroundings similar in tem-

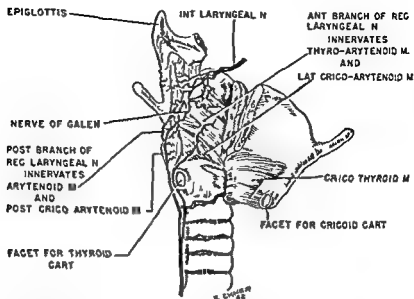


FIG 62 Lateral view of the recurrent laryngeal nerve. Note the nerve passing behind the cricothyroid articulation (Ross D & Parakk 14 of recurrent laryngeal nerve Am J Surg June 1953)

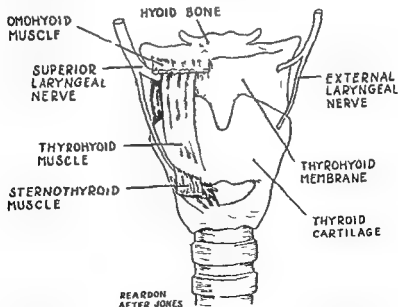


FIG 63 This drawing illustrates the position and course of the superior laryngeal nerve in an anterior view. The close proximity of the nerve to the thyrohyoid muscle is evident. Dissection of the thyroid gland in this locality presents the danger of possible nerve injury if one fails to recall the location of the nerve.

Closure of Operative Site Prior to closing the wound the anesthetist is requested to flex the patient's head. This procedure relaxes the muscles under tension and also may stimulate bleeding from any vessel insecurely ligated. Thus any bleeding point can be seen and controlled before the incision is closed.

The prethyroid muscles are approximated with interrupted mattress sutures (black silk) and accurately closed in the midline. If the muscles

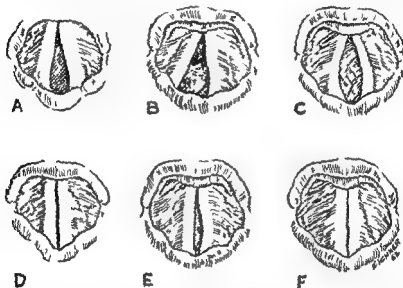


FIG 66 Anatomic position normal and abnormal of the vocal cords. A Normal larynx in inspiration. B Unilateral paralysis in inspiration. C Bilateral midline paralysis (cadaveric position). D Normal larynx in phonation. E Unilateral paralysis in phonation. F Bilateral midline paralysis (assumed in some cases) (Ross D E Paralysis of recurrent laryngeal nerve. Am J Surg June 1953)

are not approximated satisfactorily, the skin flap may become adherent to the trachea. If this does occur, the skin moves with every act of swallowing, resulting in an unsightly deformity.

Finally, closure of the wound is accomplished without drainage. If deep bleeding has been controlled with difficulty and the surgeon anticipates the possibility of bleeding, a drain should be inserted deeply into the operative site and allowed to emerge from the lateral edge of the operative skin incision.

Minor bleeding from the skin edges is usually no problem. Bleeding of this type can be controlled by metal skin clips. Metal clips do not alter the

perature and physiochemistry to those from which it came. For this reason it is best to transplant a parathyroid into the thyroid remnant. It is not definitely known how many glands must be removed before tetany occurs. However the removal of one gland usually does not result in tetany with three active glands remaining.

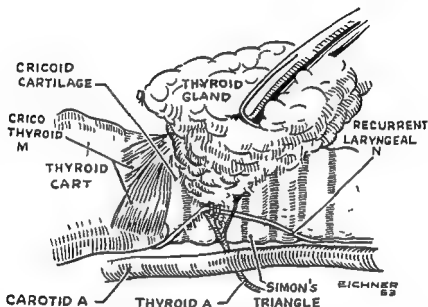


FIG. 65 This drawing illustrates how the recurrent laryngeal nerve is angulated forward in Simon's triangle by traction on the thyroid lobe. Nerve injury does not usually occur in this triangle when there is no traction, although this area is a valuable asset in identifying the nerve. However, when traction occurs, the nerve is angulated and injury may occur at the angulation point when a clamp is placed in this region. As the drawing indicates, the point of nerve injury is higher than Simon's triangle (the level of the first tracheal cartilage). (Courtesy of Donald E. Ross of Los Angeles.)

The Thyroid Remnant Following thyroidectomy, bilateral stumps of the lobes remain. Their cut surfaces are rough with minute bleeding not often visualized. In order to eliminate the rough surfaces and to control the bleeding, the remnant may be sutured against the sides of the trachea, thus eliminating the possibility of having the rough cut surface of the remnants becoming adherent to the sternothyroid muscle. Absorbable catgut is best for this type of suturing, but fine black silk may be employed as well. Tracheal sutures must be placed with care in order to prevent tracheal perforation or an excessive reaction resulting in a tracheitis.

healing of the skin flap if they are not pressed too tightly. In persons with a keloid tendency (ascertained by the presence of keloid formation in other operative scars) it is preferable to employ silk to close the skin

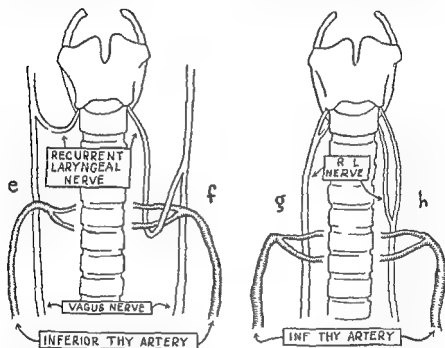


FIG 67 E Another situation in which the recurrent laryngeal nerve does not descend into the mediastinum. It makes an acute angle almost straight from the vagus nerve to enter the larynx at a level beneath the inferior constrictor muscle.

F In this drawing the nerve actually encompasses the inferior thyroid artery, descending in front of it and then going upward behind the artery. In this situation injury to the nerve is almost inevitable unless a dissection of the artery is carried out with much diligence.

G A dichotomous recurrent laryngeal nerve is here demonstrated. This is described as an extralaryngeal division of the nerve. There is seen a division of the nerve just before it enters the larynx.

H Another illustration of the same division of the nerve. However, in this drawing the extralaryngeal division is lower than in G and is closer to the inferior thyroid artery.

If the surgeon finds keloid formations on the body of his thyroid patient, radium may be used prophylactically. This form of therapy may be started 8 to 10 days following thyroidectomy. If radium does not prevent keloid formation, it may reduce the severity of it. Beveling of the skin incision and a careless, inexact approximation of the skin flap after surgery may be factors in accentuating keloid formation.

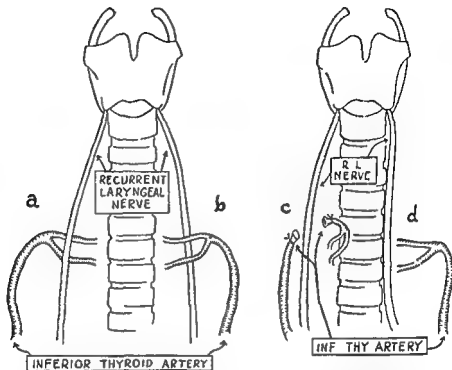


FIG 67 This series of drawings illustrates the various sites of the recurrent laryngeal nerves and the devious pathways that it may follow in relationship to the inferior thyroid artery. A knowledge of the location of this nerve will help avoid injury to it. Therefore if it is at all possible the nerve may be identified and then the surgeon can proceed without fear of damaging it.

A A portrayal of the recurrent laryngeal nerve passing anterior to the artery. When the nerve is present in this area it is more easily demonstrated and at the same time is less easily injured than when located elsewhere (i.e. when the nerve passes posterior to the artery). In this location the nerve is lifted with the gland when it is retracted anteriorly and medially out of its bed. Attempts at identification and ligation of the inferior thyroid artery therefore may inadvertently result in clamping, cutting or ligating the recurrent laryngeal nerve.

B This is the most frequently seen location of the recurrent nerve as it rests behind the inferior thyroid artery. Dissection and demonstration of the inferior thyroid artery and its ligation will reveal the underlying nerve.

C This diagram demonstrates the division of the inferior thyroid artery. As a fundamental principle it is well to remember that the nerve is almost always found in relationship to the artery. Therefore in a difficult situation identification and division of the artery may often facilitate the demonstration of the recurrent nerve as it emerges from the mediastinum and proceeds upward into the larynx.

D This drawing shows the position the recurrent nerve may take in patients with large cervical substernal and intrathoracic goiters. As the goiter increases in size it gradually compresses the recurrent laryngeal nerve against the trachea. Clinically this may produce voice changes. At the operating table the nerve may be so close to the trachea that it is adherent to it. This makes identification and demonstration of the nerve most difficult and often impossible.

healing of the skin flap if they are not pressed too tightly. In persons with a keloid tendency (ascertained by the presence of keloid formation in other operative scars) it is preferable to employ silk to close the skin

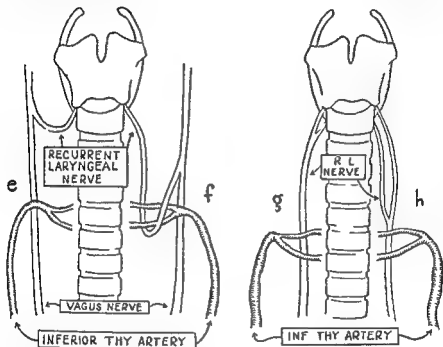


FIG 6 E Another situation in which the recurrent laryngeal nerve does not descend into the mediastinum. It makes an acute angle almost straight from the vagus nerve to enter the larynx at a level beneath the inferior constrictor muscle.

F In this drawing the nerve actually encompasses the inferior thyroid artery descending in front of it and then going upward behind the artery. In this situation injury to the nerve is almost inevitable unless a dissection of the artery is carried out with much diligence.

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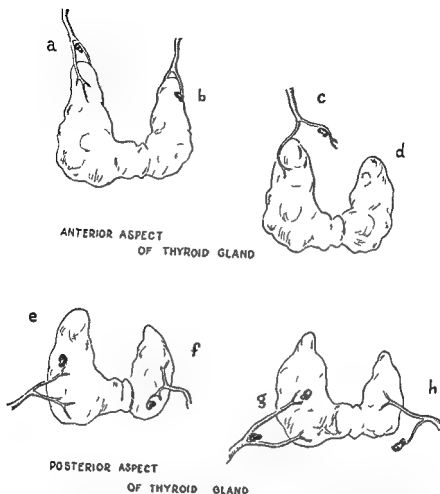
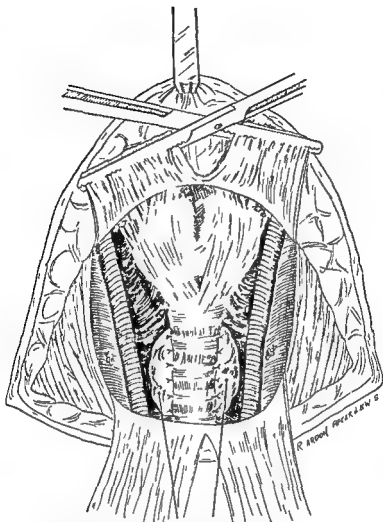


FIG 68 These drawings show the positions of the parathyroid glands on the anterior and the posterior aspects of the thyroid gland. In general, the parathyroid gland is in the vicinity of an artery. In figure D the incomplete dotted area represents a parathyroid gland close to the larynx. In this location the gland can be removed with the thyroid tissue and go undetected. Figure H depicts a parathyroid gland as an appendage to the terminal branch of an inferior thyroid artery. It is well to remember figures A to H when one explores the neck for a parathyroid adenoma. In such cases it is an aid to realize that the tumor is close to an artery. Secondly, that if the adenoma cannot be found, then the inferior thyroid artery should be traced throughout its entire course. All the branches should be followed with care given to the branches going in the direction of the mediastinum. A parathyroid adenoma is frequently found in the superior mediastinum. Thirdly, figures E to H illustrate the location of the parathyroid glands on the posterior aspect of the thyroid gland. The arteries may be the sites for an adenoma. For this reason, a complete exploration of the neck for a parathyroid adenoma may necessitate a division of the thyroid isthmus and a lateral release of the right and left lobes in order to prove or disprove the presence of the tumor at this location.



REMNANTS OF THYROID GLAND
SUTURED TO TRACHEA

FIG 69 When both lobes of the thyroid have been removed and also the pyramidal lobe (when it is present) the remnants are sutured to the trachea. These remnants are approximated close to the trachea with fine 00 catgut or fine black silk (our preference is to use black silk throughout). Suturing of these remaining thyroid areas to the trachea controls any bleeding from the gland and will prevent secondary delayed hemorrhage. Note the ligated stumps of the middle thyroid veins bilaterally.

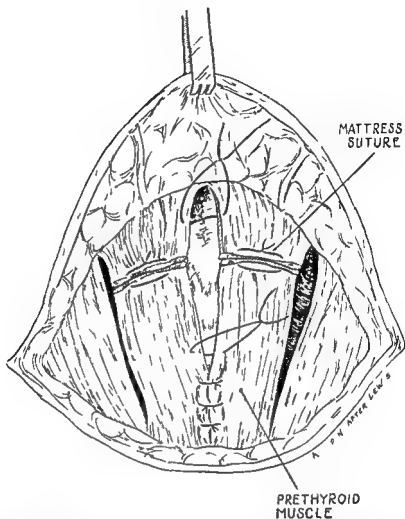


FIG. 70 When no bleeding is in evidence and the head has been flexed then the muscles are reconstructed. The prethyroid muscles are approximated with mattress sutures of silk. The muscles are sutured in the midline with interrupted single black silk sutures. A satisfactory closure of the muscles is one in which there is no irregular surface which may become adherent to the skin and no visible trachea which could adhere to the skin flap. When the skin is closed with metal clips the sutured muscle is high above the line of clips.

Treatment of Post-Thyroidectomy Tetany

Tetany following thyroidectomy may be latent or manifest. When it manifests itself, it usually occurs on the second postoperative day. It may occur sooner if the blood calcium levels fall rapidly. The clinical revelation of tetany demands that some measures be instituted to counter

act this distressing complication. In the treatment of tetany calcium salts, parathyroid hormone and dihydrotachysterol have been used. A product of value is Hytakerol which is prepared in oil and in capsules for oral administration. When given orally the dose is 6 to 20 capsules daily (or 3 to 10 cc parenterally) according to the severity of the tetany. The drug is given until the tetany is relieved. On occasion a weekly maintenance dose is needed (2 to 14 capsules or 1 to 7 cc) depending upon the blood and urine calcium level which should be determined at stated intervals. During the course of Hytakerol therapy calcium lactate or gluconate (from 10 to 15 Gm) should be given daily. Patients with tetany are ad-

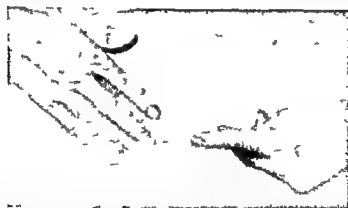


FIG. 41 The characteristic attitude of the hand in tetany. The fingers of the left hand are flexed at the metacarpophalangeal joints and extended at the interphalangeal joints. The thumb is adducted across the palm of the hand. Right hand is normal and is shown for comparison (Graham F. A. Surgical Diagnosis Philadelphia W. B. Saunders Co. 1930)

vised to drink milk in large quantities. Tetany following thyroidectomy is usually transient in type and of short duration.

It has been demonstrated experimentally that the blood supply to the parathyroid gland is not disturbed even after the ligation of all four thyroid arteries. ⁶⁹ The abundant collateral circulation established between the internal laryngeal, internal mammary and the transtracheal vessels together with the preservation of the posterior facial layers over the trachea allows for an adequate blood supply to the parathyroid glands. For this reason the surgeon does not fear ligating the major vessels going to the thyroid gland because he is aware of the fact that he cannot injure the parathyroid glands in this way. One should see however that the parathyroids are not removed accidentally in the operative specimen.

It is possible that a patient may develop chronic hypoparathyroid tetany following thyroidectomy.

Case report. A case of this type in a 54 year old woman has been reported by Blackburn in the Medical Journal of Australia (1 978-93? 1954). He treated this patient satisfactorily and controlled her tetany by placing her on a diet of low phosphorus and calcium content. In addition he gave her the following medication: calcium lactate 10 to 20 gm. daily (3 to 6 tea spoon full) to ensure a high calcium intake and to compensate for the calcium poor diet. Dihydrotachysterol (1 T 10) was given in doses of 2.5 mg. (2 cap. ules of 1.25 mg.) daily with Amphojel, a proprietary colloidal suspension of aluminum hydroxide. The excellent and well maintained biochemical response of the patient and her clinical improvement were striking. On various occasions changes were made for investigative purposes in the dosage of dihydrotachysterol. It was found that the serum calcium level rapidly fell and tetany developed when dihydrotachysterol with added calcium was withheld. Her serum calcium level rapidly returned to normal or above when treatment was reinstituted. After 2 years of treatment with dihydrotachysterol, vitamin D in doses of 100,000 units daily was substituted for dihydrotachysterol without significant disturbance in her serum calcium or serum phosphorus levels. Calcium and serum phosphorus determinations were made frequently on this patient.

The dangers of hypercalcemia cannot be overemphasized. Patients may take calcium and vitamin D for years without incident but in some, hypercalcemia may develop rapidly.

A patient with carpopedal spasms was given a diet low in phosphorus and calcium content. Also given was 150,000 units of vitamin D, 15 gm. of calcium gluconate and 9 teaspoonful of Amphojel daily. One month later her calcium intake was increased by discontinuing the calcium gluconate and starting the administration of 20 gm. of calcium lactate daily. She was maintained well and with normal serum calcium concentrations for the next 6 months. An acute episode of hypercalcemia was observed 23 months after the institution of treatment with calcium and vitamin D and all antitetany treatment was stopped. Her condition improved as her serum calcium level fell. Two weeks later treatment was recommenced with the daily administration of 50,000 units of vitamin D and 12 gm. of calcium lactate. However her serum calcium level rose to 13.1 mg./100 cc. in 14 days and therefore all antitetany treatment was suspended for 6 months. She is now maintained in a clinically and biochemically normal condition on a diet of low calcium and phosphorus content, 20,000 units of vitamin D and 6 gm. of calcium lactate daily. No reason for this patient's hypercalcemia can be suggested other than that some remaining parathyroid tissue has resumed secretion. This supposition is supported by the fact that a small dose of vitamin D is now required to maintain the patient's serum calcium level.

Adequate treatment will eliminate acute attacks of tetany, and the chronic complications will not occur. The necessity for close control of treatment by frequent serum calcium determinations and for continuing treatment for the rest of the patient's life is stressed.

12

Complications during and after Thyroidectomy

TODAY, COMPLICATIONS following thyroid surgery are the exception rather than the rule. When they do occur, however, both the surgeon and the patient become quite disturbed. Their uneasiness is justified because the failure to recognize and treat most of the complications may result in death. Fortunately, in the light of modern knowledge, many of the complications can be prevented.

The complications following thyroidectomy fall into the following categories:

- 1 Recurrent laryngeal nerve injury
- 2 Parathyroid removal (tetany)
- 3 Hemorrhage
- 4 Tracheal injuries or collapse
- 5 Cardiac disturbances
- 6 Air embolism
- 7 Anesthetic complications
- 8 Thyroid crisis
- 9 Noninflammatory edema of the larynx

Careful, meticulous surgical technique during a thyroidectomy will in a great measure prevent certain complications. Specific reference is made to injury to the laryngeal nerves or removal of the parathyroid glands. Both these subjects have been discussed in detail under surgical procedures.

Hemorrhage is the infrequent complication of the experienced thyroid surgeon. It is, however, a very grave fear of the occasional operator. Most often this bleeding arises from the lateral or median veins. The vessels may be friable (especially in the elderly) and are easily torn by blunt dissection or when the surgeon elevates the thyroid lobe. Ligation of these veins prior to manipulating the gland will eliminate the possibility of hemorrhage from these vessels. The thyroid arteries do not usually bleed after surgery if double ligation is accomplished (cf. discussion of arteries under surgical technique).

Postoperative hemorrhage occurring within a few hours after operation is a tragic drama in itself. When it develops the patient may become rest-

room in satisfactory condition. This includes a dry gown for the patient and team inhalations in the patient's room if it is deemed necessary.

Thyroid crisis has been mentioned previously. Suffice it to say at this point that proper preoperative preparation of the patient with the anti-thyroid drugs and iodine should prevent any exacerbation of acute hyperthyroidism or thyroid crisis.

Recently patients have been prepared for thyroidectomy with a new type of iodine preparation. This iodine is contained in a capsule. Each capsule contains 150 mg. (two and one half gr.) of iodine organically bound and is equivalent in iodine content to 100 minims of organiodin solution. The capsules are administered 1 or 2 a day for 2 weeks prior to operation. The glands of these patients prepared with this new capsule were ideal for surgery. They were well involuted, firm and did not develop any adhesions to adjacent structures. The patients themselves did not object to this method of iodimization since they had no iodine taste which is often the complaint when iodine is given in liquid form.

Noninflammatory edema of the larynx may be a manifestation of iodism. This type of edema may occur following surgery. It is usually transitory in type and disappears within 1 week. A similar type of noninflammatory edema may occur in myxedema following thyroidectomy. The general systemic reaction of myxedema causes the laryngeal edema and is the expression of the generalized complication. The correction of the myxedema eliminates the laryngeal edema and this complication evaporates under proper therapy. On occasion during the postoperative period noninflammatory edema of the larynx may be confused with laryngeal obstruction. However if one remembers that croupy cough, stridor, wheezing, dyspnea and difficulty in breathing are typically manifestations of obstructive laryngeal dyspnea, the differential diagnosis can be made.

From this discussion on complication during and after thyroidectomy, one fact remains in evidence. Most complications can be avoided if the surgeon prepares the patient properly for surgery, performs a careful thyroidectomy and personally supervises the postoperative management.

Immediate Postoperative Care

After thyroidectomy the following is prescribed:

1. The patient is given intravenously 5 per cent glucose in water or saline depending upon the age of the patient and whether or not he has lost salt via perspiration.
2. Sodium iodide (15 gr.) is given in the intravenous glucose.
3. An ice collar is placed about the neck for 24 hours. This prevents serum accumulation and diminishes edema.

less Progressive dyspnea with an associated cyanosis is noted as the fullness of the neck due to the accumulating blood pressure on the trachea. Dyspnea may be so insidious that the patient passes from a state of anoxemia to unconsciousness very rapidly. This type of patient demands immediate assistance. The skin clips or silk sutures should be removed and the underlying incarcerated blood clots liberated. Blood clots may gush out or may be removed manually. The source of the bleeding is detected and controlled with a ligature if necessary. This type of bleeding may be more difficult to control than the performing of an entire thyroidectomy.

Injury to the trachea is not a very serious complication when compared to postoperative hemorrhage. If the trachea is cut, several sutures may be used to approximate the laceration. A small rent may be covered with a muscle transplant. Tracheal collapse is a more serious complication and may occur during or immediately after operation. The danger of this complication is in patients with large cervical goiters, intrathoracic goiters or retrotracheal goiter (or a combination of all three types). Tracheotomy is a life saving procedure in such cases. More specific information on this topic may be found on page 180.

Cardiac disturbances may be either cardiac failure or arrhythmia. The problem of arrhythmias following thyroidectomy will be discussed subsequently. The development of congestive heart failure during or following thyroidectomy should not occur if the patient is prepared properly for thyroidectomy. This complication has never occurred in my own experience although such cases have been presented at hospital conference.

Air embolism is a rare complication which is seldom seen but which has been discussed by excellent thyroid surgeons. Air embolism occurs usually when surgery has been completed and the dressing is being applied. The patient coughs (often violently) and there follows a noise like air escaping from a tire. Cyanosis rapidly occurs and the patient dies immediately. It is conjectured that the violent coughing loosens the ligature of a vessel and then air is aspirated.¹⁴¹ When an air embolism occurs the patient's head should be lowered to the floor.

In the past anesthesia complications were avoided by the thyroid surgeon by employing superficial nerve block and the ia. In this modern age anesthesia is administered by a competent physician anesthetist. No longer should more complications be anticipated in the thyroid patient than in one undergoing a laparotomy. At one time cyclopropane and the ia was used and many patients developed cardiac irregularities. Cyclopropane is not commonly used in thyroid surgery today. Pneumonia and atelectasis rarely occur when a definite postoperative routine is followed. Every surgeon should personally see that his thyroid patient leaves the operating

The presence of auricular fibrillation has been an indication for administering some drug to control the irregularity. Digitalis does not possess the property of re-establishing normal rhythm in patients who have auricular fibrillation. In the 11 patients mentioned quinidine lactate or quinidine sulfate was employed with excellent results. If a patient has had an embolic accident quinidine should not be administered. When quini-

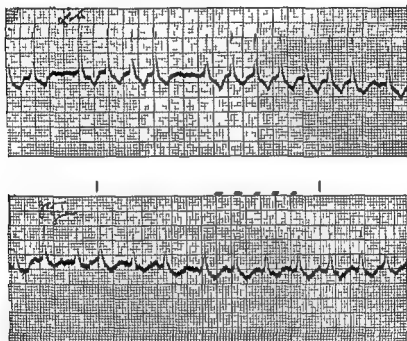


FIG 7^o Electrocardiogram of a patient with thyrotoxicosis showing auricular fibrillation (leads I and II). This patient had a preoperative BMR +45 and a total cholesterol of 150 mg per cent. This is the commonest type of arrhythmia seen in thyrotoxicosis. (The small oscillations are designated f waves or fibrillatory waves.)

dine lactate is given the same precautions should be taken as when quinidine sulfate is employed for this cardiac arrhythmia. The patient must be observed closely and should remain in bed for 24 hours after the last dose of quinidine. As soon as the fibrillation is discovered the patient is given quinidine (prescribed by a cardiologist).

The best results seemed to be obtained when the drug was given at an interval of 2 hours between doses. On the first day 2 doses of 0.2 Gm were given as a test for hypersensitivity. If no symptoms developed 5 doses of 0.4 Gm were given on each of the following days.

Since the completion of the survey 6 patients have been seen with

- 4 Syrup of hydriodic acid (2 dr) is given every 4 hours as soon as the patient can take it orally. This is an excellent liquefying expectorant.
- 5 The patient is placed in a sitting position as soon as possible.
- 6 The patient is allowed out of bed and eats a regular diet the day after surgery.

A few words of explanation are in order on the use of sodium iodide postoperatively. This drug is not given for any reason other than that it is a liquefying expectorant. It enables the patient when reacting to eliminate any mucus plug which may accumulate in the respiratory tree. Hydriodic acid is given for the same reason during the immediate postoperative period.

Transient Cardiac Arrhythmia following Thyroidectomy

A purposeful survey was made of 100 consecutive thyroid procedures to determine cardiac arrhythmias. Sixty of these patients had primary hyperthyroidism (toxic goiter). Of these only 9 had true hyperthyroid heart disease, determined preoperatively. Thus 51 patients with severe hyperthyroidism did not have any cardiac disturbance which was demonstrable prior to operation. Following thyroidectomy, however, 11 of the 60 patients developed cardiac irregularities which were determined by clinical auscultation and corroborated by electrocardiogram. The arrhythmia encountered was auricular fibrillation.

Disturbance in the rhythm of the heart is a common occurrence in patients with hyperthyroid heart disease. However to find auricular fibrillation developing after thyroidectomy in patients without a pre-existing arrhythmia is not the usual pattern of events. The postoperative presence of auricular fibrillation could not be interpreted as a cyclopropane arrhythmia since this drug was not employed for anesthesia.

Although auricular fibrillation may occur in young people as a purely functional disorder, it is usually associated with organic heart disease. Especially is this true in hypertensive, rheumatic and hyperthyroid heart disease. Auricular fibrillation is characterized by an absolute irregularity of the heart and the entire absence of an underlying basic rhythm. This was the situation with the 11 patients following thyroidectomy.

The exact time of onset of this irregularity postoperatively could not be determined. However it was noted within 6 and 9 hours following the patient's return from the operating room. In all instances the arrhythmia was discovered during evening rounds (about 5:00 or 6:00 P.M.) on the same day of operation which usually commenced at 8:30 A.M.

tracheotomy which is never open to dispute is postoperative tracheal obstruction secondary to hemorrhage. Emergency tracheotomy in the emergency cases is imperative for the preservation of life. Elective tracheotomy following thyroidectomy however presents a different problem. The question as to when this procedure is indicated may be open to dispute.

An elective tracheotomy is advocated in those patients with large colloid goiters producing tracheal compression and/or marked tracheal deviation. This is especially true when there is subternal extension of the gland. In the case presented here a satisfactory outcome would have been impossible without an elective tracheotomy. When there is a question as to whether or not to perform a tracheotomy and doubt exists I prefer to do the tracheotomy.

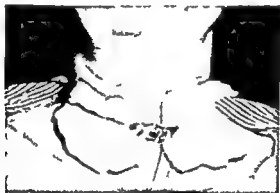


FIG. 3. Elective tracheotomy following thyroidectomy for massive subternal colloid goiter.

Case report. The patient M. B., 36 years of age, was seen in May, 1947. He presented the history of a swelling in the neck of ten year duration. During the past six months this had increased in size and more recently, over a period of several weeks, he had developed hoarseness and dyspnea on exertion. Because of the hoarseness and dyspnea, he was referred for surgical treatment. Physical examination at that time revealed an obese man weighing 250 pounds. His blood pressure was 190/100, pulse 100, B.M.T. plus 16. The significant findings were referable to the thyroid gland. The gland was enlarged to twelve times normal size. Preoperative x-ray study revealed tracheal deviation to the left and a subternal extension of the thyroid into the mediastinum. The patient talked with difficulty and displayed hoarseness which was his chief complaint. The patient was prepared for operation and subjected to a total thyroidectomy and elective tracheotomy on May 21, 1947. He had an uneventful recovery. The tracheotomy tube was removed on the second postoperative day and the patient was discharged from the hospital one week after his operation.

As demonstrated by this patient, the large thyroid gland displaced the trachea. Displacement of this type is conducive to diminution in the exchange capacity of the tracheal airway. Such insufficiency may precipitate

auricular fibrillation following thyroidectomy. These 6 patients did not receive quinidine or any other drug aimed at arresting the arrhythmia. All 6 patients had a disappearance of the auricular fibrillation from 2 to 4 days after thyroidectomy. It seems therefore that this type of auricular

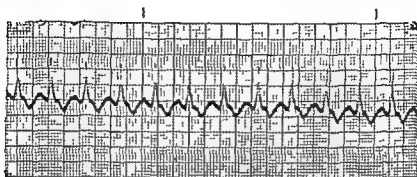


FIG 73

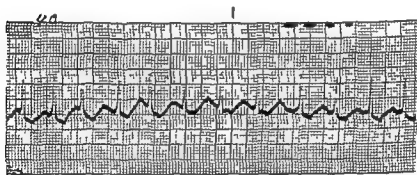


FIG 74

FIG 73 Electrocardiogram of the same patient after the administration of quinidine (8 gr). Changes noted in F waves indicate a lowering of conduction time which is a typical quinidine effect.

FIG 74 Electrocardiographic tracing taken 24 hours after the first recording. There was no change in rhythm in the tracings taken subsequently on the second and third postoperative days. Most cardiac arrhythmias due to thyrotoxicosis disappear spontaneously following thyroidectomy.

fibrillation is transient in type, functional in origin, and does not necessitate specific drug therapy.

Elective Tracheotomy Following Thyroidectomy

Surgeons who operate on many thyroid patients are frequently confronted with the problem of performing a tracheotomy. An indication for

field is obtained and the cervical portions of the thyroid can then be resected easily. If the subternal and intrathoracic portion of the goiter can not be removed easily through the cervical incision then an intrathoracic approach to the goiter must be made. Under this circumstance the goiter may be removed in one or more of the following methods:

- 1 Manual removal through the superior thoracic outlet
- 2 Separation of the sternoclavicular joint

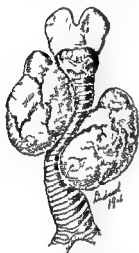


FIG. 6



FIG. 7

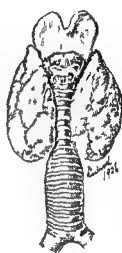


FIG. 8

FIG. 6 Diagrammatic illustration showing compression of the trachea between two enlarged lobes of the thyroid gland at different levels. The trachea is distorted into an S-shaped tube with a diminution in caliber at the compression site and dilatation below the obstruction.

FIG. 7 Tracheal compression secondary to a unilateral thyroid enlargement.

FIG. 8 Bilateral tracheal compression due to a symmetrical enlargement of the thyroid gland at the same level. Beneath the compression site is the characteristic dilatation found below the point of obstruction.

- 3 Division of the manubrium and/or the sternum
- 4 Thoracotomy especially in goiter plongeant

Manual liberation and removal of an intrathoracic goiter from adjacent mediastinal tissue can be accomplished via digital dissection. The index finger is inserted into the mediastinum outside the capsule of the adenomatous. This procedure is continued around the entire exterior surface of the goiter as far as possible. Little bleeding is encountered since this area forms a natural line of cleavage between the goiter, the pleura, and mediastinal tissue. This procedure of digital dissection is the initial step in

anoxia. This may increase a previously existing anoxic state which is characteristic of patients with hyperthyroidism. Anoxia is further increased if a mucus plug occludes a major or minor bronchus. Tracheotomy establishes an artificial airway which eliminates the incipient anoxia.

Often large goiters in addition compress the recurrent laryngeal nerve. Following the removal of the offending pathology, edema occurs about the site of compression. This edema may result in transitory paralysis of one or both vocal cords. Paralysis disappears when the edema subsides. In this instance a tracheotomy is indicated until the edema has subsided.

Substernal and Intrathoracic Goiter

Approximately 1 per cent of adenomatous colloid goiters are within the thorax. Twenty-five per cent of adenomatous goiters are substernal in location. An examination of the neck in a patient with a substernal or intrathoracic goiter reveals dilated veins which may extend superiorly and even inferiorly on to the chest wall. The patient usually seeks relief because of dyspnea. Raspy breathing inpiration, stridor, choking and coughing often suggest the diagnosis before the patient declares his symptomatology. Motions of the neck such as sudden flexion or extension or motion to the right or left will produce coughing or choking. This is due to compression. In extreme situations the trachea may collapse and death may occur before the patient is prepared for surgery. When an intrathoracic goiter does not compress any important structures no obvious sign or symptom may be noted. The presence of this intrathoracic mass may be visualized only by roentgen examination of the chest.

It is not uncommon for the recurrent laryngeal nerve to be under tension or even paralyzed by an intrathoracic goiter. When this occurs aphonia may result. Complete or partial paralysis of the vocal cords may be produced by the displacement of large cervical blood vessels which is caused by enlargement of an intrathoracic goiter.

In addition to the compression resulting from large goiters in the neck, tracheal and/or bronchial compression may also result from substernal or intrathoracic goiters. Surgery is then necessary to relieve the embarrassed respiration. Often substernal and intrathoracic goiters cannot be removed easily through the usual cervical incision. When the incision is made one must be aware of the fact that exposure is more important than the cosmetic effect or the plastic result. It is well to bear in mind that the best location for the incision is lower than that usually made. It should be parallel to a normal flexion crease of the neck. The smaller lobe or lobes of the thyroid are usually removed before the superior thyroid vessels are identified and ligated. After ligation of the superior thyroid artery a dry

Phantom Gouter

During the past eighteen years and more many private and ward patients with thyroid disturbance have been examined, managed and or treated. Of all the patients three have made an indelible impression upon me. All three were elderly women with a history quite similar in all three cases.

Their troubles were those of large cervical adenomatous goiters of many years duration which were untreated until compression symptoms developed in the neck region. At this stage they were seen by their respective family physicians who prescribed iodine solution. The iodine caused an involution of the thyroid tissue present in the goiter with a resultant diminution in the size of the goiters. This decrease in size was sufficient to allow the goiters to drop by their own weight behind the sternum or behind the clavicles. The goiters either ceased to be visible completely or diminished in size so that they were no longer prominent. The patient thought that the goiters had disappeared overnight like a phantom spirit.

The facility with which a goiter can gravitate into the chest is understandable when one considers that the adenomatous goiters possess many areas of cystic degeneration. These areas are readily compressible and hence can pass through an inlet much smaller than the mass itself. The descent of these goitrous masses is deeper behind the sternum than when they are located behind the clavicle. The reason for this is that there is Sibson's aponeurosis behind and above the clavicle but it is absent behind the manubrium sterni.

Sibson's aponeurosis is named for Francis Sibson an English anatomist (1814-1876) is in reality a vertebropleural ligament attached to the seventh

FIG. 80—Continued

The lower diagram demonstrates tracheal deviation resulting from an intrathoracic adenoma. Digital and manual removal of such an adenoma necessitate its liberation from adjacent tissue as well as the pleura. There is danger here of perforating the parietal pleura. After separating the adenoma from contiguous structure it can be grasped with thyroid clamps and lifted out of the mediastinum to the level of the clavicle. The top of the adenoma can then be incised and removed (decapitation). The inner contents of the adenoma are thus exposed and found to be soft indicating an adenomatous colloid goiter. If the mass is hard it is usually carcinoma and most likely an inoperable lesion. When the mass is found to be soft it is usually cystic with necrotic tissue which can be crushed easily with the finger and removed with a gall bladder scoop. Suction may also be used. Removal of the interior contents of the adenoma diminishes the size of the goiter markedly. The capsule is then grasped again with thyroid clamps and retracted superiorly out of its bed. Further dissection of the exterior aspect of the capsule from contiguous structures will gradually liberate the entire mass. This procedure is satisfactory in most instances and will eliminate the necessity for dividing the sternoclavicular joint.

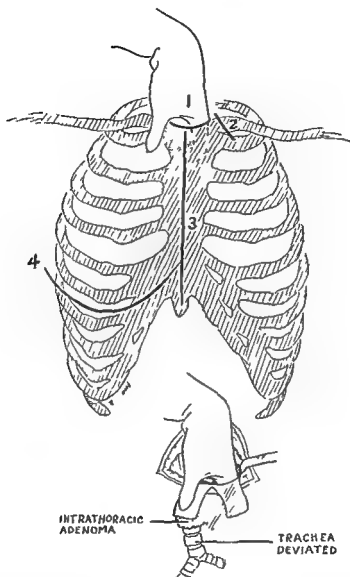


FIG 80 Diagram illustrating the methods of removing substernal and intrathoracic goiters

- 1 Manual and digital removal through the superior thoracic outlet
- 2 Separation of the sternoclavicular joint when the goiter is fixed in the superior mediastinum
- 3 Division of the manubrium and/or the sternum to remove goiters fixed in the anterior middle mediastinum and those which cannot be reached through the superior mediastinum
- 4 Thoracotomy when the goiter is intrathoracic and appears similar to a pulmonary tumor as in goiter plongeant

Complications of Tracheotomy

The performance of a tracheotomy is not free from hazard. A decision not to do a tracheotomy often has been influenced by the fear of complications. These complications may occur as (1) infection (2) emphysema (3) pulmonary infection or (4) tracheal stenosis.

Infection Tracheal secretions emanating from the tracheotomy tube carry organisms into the operative site. This may produce a wound infection. When silk is used for ligatures infection is a serious complication. Sepsis is diminished if the dressings are changed every half hour during the first 24 hours. Infection can travel subcutaneously and produce a mediastinitis. As a prophylaxis against this a generous gauze pack is employed to block off the mediastinum. Penicillin is given parenterally during the period in which the tracheotomy tube is in situ. In some cases the patients develop thick sputum which threatens to block off the tracheotomy orifice. This is controlled by penicillin inhalation as a supplement to the intramuscular dosage.

Emphysema Air escaping about the tracheotomy tube may result in emphysema. If air accumulates beneath the skin subcutaneous emphysema results. Mediastinal emphysema develops when air dissects under the deep cervical fascia. Intubation produces a normal negative pressure which will increase the spreading power of the air. If the mediastinal emphysema continues it may reach the pleural cavity causing a pneumothorax. The best preventive measure against the development of emphysema is packing. The wound should be packed widely and left open.

Pulmonary Infection The least probable complication is the development of pneumonia or edema. Constant attention to the tracheotomy tube with frequent aspirations employing an adequate suction apparatus will prevent the aspiration of mucus which could stimulate an infection or produce an atelectasis. If the need arises penicillin can be instilled into the respiratory tree and the tracheotomy tube.

Removal of the Tube The trachea is a resilient organ and readily returns to its proper anatomic location. For this reason a tracheotomy tube is employed for 1 or 3 days. 3 days is the longest time. The presence of complications however may necessitate leaving the tube in place longer than usual. Prior to removing a tracheotomy tube an x-ray of the chest should be taken. This will demonstrate any fluid accumulation in the sub-sternal space which may be the source of future tracheal compression. In the event that the fluid may be old blood no damage is anticipated if the blood is clotted. A large blood clot may be identified by placing a stethoscope over the area. A friction rub similar to a pericardial friction rub will be heard. The presence of this sound indicates that the tube may be

cervical vertebra above and the dome of the pleura below. This ligament supports and strengthens the dome of the pleura. For this reason a 'falling' or phantom goiter cannot descend too far behind the clavicles because the dome of the pleura plus a supporting structure in the nature of an aponeurosis is present. This same aponeurosis can become attenuated over a period of time (years) due to a large goiter pressing on it from above associated with a continual respiratory action of the lung and pleura constantly producing friction against it. Physiologic activity of this type inevitably results in an attrition of the structure involved and hence it attenuates Sibson's aponeurosis.

Following the surgical removal, therefore, of a subclavicular goiter on either the right or left side there results a visible herniation through Sibson's aponeurosis. This swelling results from an increase in the expansion of the underlying lung parenchyma which is no longer compressed by an overlying goiter. Hence it is that some patients will call attention to this swelling weeks after thyroidectomy. An explanation of the pulmonary mechanism will relieve the patient of this anxiety even as it will dispel the impression that the goiter was not removed in toto or that it is recurring so soon after surgery.

Tracheotomy and Thyroidectomy

At the time of thyroidectomy tracheotomy is a simple procedure. The trachea is cleansed of thyroid tissue and the cartilaginous rings are clearly visible. The site of election is usually below the second cartilaginous ring because high tracheotomy may produce laryngeal edema which may result in a stenosis. High tracheotomy is more apt to cause perichondritis for the same reason. Moreover high tracheotomy results in difficult decannulation. For these reasons the fourth cartilaginous ring is the preferred level.

A vertical incision is made in the center of the fourth cartilaginous ring with a #15 bladed scalpel. This is usually sufficient. However on occasion a small segment of cartilage may be removed in order to facilitate the entrance of the tracheotomy tube. With the stylette in situ the tracheotomy tube is inserted into the trachea. The membranous portion of the trachea relaxes sufficiently to enable the cartilaginous ring to spread.

A plain half inch gauze pack is then placed on either side of the tracheotomy tube. The stylette is removed and the tracheotomy is allowed to function on the operating table. Anesthesia is generally discontinued at this stage. Since patients with substernal goiter are usually given intra-tracheal anesthesia tracheotomy necessitates the removal of the endotracheal tube.

13

Thyroid Cancer

A study of primary carcinoma of the thyroid gland demonstrates that these carcinomata are a heterogeneous group of tumors of markedly different histological structure and biological behavior. In addition these carcinomata are relatively uncommon. Because of this fact many years passed before there was a sufficient number of recorded cases to make possible a correlation of histological pattern of various thyroid cancers and the clinical course and biological activity of these lesions. Until a harmonious relationship was established between the histological picture and the biological activity of thyroid cancer there was much confusion and indecision about the subject of thyroid cancer. From the pathological point of view the less anaplastic carcinomata particularly were surrounded by a nebulous uncertainty. The benign histological appearance of these anaplastic lesions or their apparently benign course was at variance with the then current concept regarding carcinoma. In preceding decades these tumors were treated as benign lesions. For this reason the only primary carcinomata recognized were the more anaplastic type. The treatment for these lesions at that time was most unsatisfactory. In view of this inadequate therapy there was much pessimism regarding the prognosis in patients with thyroid carcinomata. As with many other malignant lesions unless there are better diagnostic or therapeutic methods available there is continual doubt that the ultimate result in the treatment of anaplastic thyroid lesions will be improved. However management of other types of thyroid cancer with present day therapeutic methods offers a better prognosis to the patient provided of course that the tumor is not inoperable at the time of diagnosis. It must be remembered that the present day attitude toward the removal of nodular goiters and all nodules in the thyroid gland will undoubtedly materially reduce the occurrence of thyroid carcinoma. It should also reduce the number of patients who will be found to be inoperable as time passes. Undoubtedly our increasing knowledge of thyroid cancer will unquestionably contribute to the ultimate better prognosis in patient afflicted with this disease.

The pathological classifications of thyroid cancers have been confusing on many occasions. From the point of view of therapy the pathological slide is of importance only insofar as it identifies the type of cancer. Cope

removed since the blood is solidified. If serosanguinous fluid is present it must be aspirated before removing the tracheotomy tube.

The procedure employed prior to the removal of the tube is to de-functionalize the tracheotomy. This is done simply by inserting the stylette into the tracheotomy tube so that it is functionless. If the patient can tolerate this occlusion for 12 hours it is safe to remove the tracheotomy tube. The tube should be removed only when the possibility of any complication has been eliminated.

Tracheal Stenosis. Cicatricial tracheal stenosis may be a delayed complication following tracheotomy. This complication may result from a high tracheotomy, a malfitting cannula or infection. The stenosis results from erosion of the tracheal mucosa, perichondritis and chondral necrosis. The subsequent cicatrix produces varying degrees of stenosis and leads to respiratory difficulty. This complication may be avoided by performing a tracheotomy below the second ring of the trachea at least. An adequate cannula fitting comfortably in situ and the combating of infections with the various antibiotics are further prophylactic measures which can prevent cicatricial tracheal stenosis. Formerly, the treatment of cicatricial stenosis of the larynx and trachea was extremely difficult. The result was that the patient often was compelled to accept permanent tracheotomy, continuous respiratory disability and even death. However at the present time the following methods are now available for the relief of this distressing stenosis:

- 1 Endoscopic dilatation
- 2 Laryngotomy or tracheotomy with incision or excision of the scar and insertion of a dilator or a free skin graft on a mold of plastic sponge
- 3 Resection of the larynx or trachea with immediate anastomosis
- 4 Resection of the trachea or bronchus with reconstruction

lary cancers are slow growing but metastasize early to the lymph nodes where the tumor may remain for months or years. Since they invade slowly and remain in the lymph nodes for a long time radical surgery offers a good prognosis.



FIG. 89 Microscopic section showing papillary carcinoma of the thyroid

3. A hybrid type of thyroid cancer often called "benign metastasizing goiter" or metastasizing adenoma has been mentioned in the literature. The primary thyroid lesion appears to be benign but distant metastases may occur in the bones (it avoids the lungs). This type has been reported in the later decades of life. Hurthle cell adenomata may belong to this group.

Cope of Boston has called attention to a node which appears in the neck either as a complication to malignant disease or in thyroiditis.⁸⁷ This node may be felt on the trachea just above the thyroid isthmus. The presence of this node is constantly indicative of these conditions so much so that Cope has called it the "Delphian node" after the classical oracle at Delphi.

has suggested that what really concerns us in the treatment of cancer is the biological behavior of the tumors.⁸⁷ This seems to be a very rational approach to the problem.

A survey of thyroid cancer from the biological point of view collects these cancers into three groups

Carcinoma of the thyroid

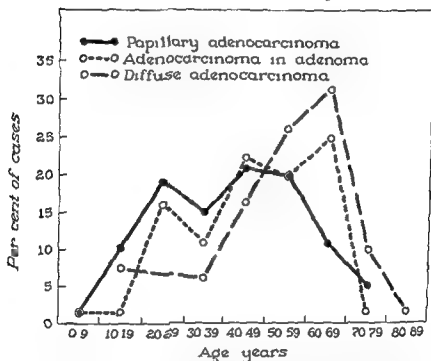


FIG. III Age distribution of carcinoma of the thyroid gland. The occurrence of papillary lesions in children and young adults is not unusual. However, contrary to erroneous impressions, the age distribution of carcinoma of the thyroid is not greatly different from that of carcinomata elsewhere in the human body. (Courtesy of the Mayo Clinic, Pemberton J. and Black B. M. Cancer of the thyroid. American Cancer Society Bulletin 1954.)

1. Thyroid cancer similar to that seen elsewhere in the human body, i.e. a disease of the middle age and the geriatric group. In this group are found the undifferentiated cancers and adenocarcinomas.
2. The commonest form of thyroid malignancy is papillary adenocarcinoma. These cancers of the thyroid are encountered in children and adults and are distributed equally in all decades of life. They are no more malignant in children than in adults. The papil-



Fig. 84 Carcinoma of the thyroid gland displacing the trachea to the left (T) C
 10115 cervical lymph nodes resulting from regional metastases (Graham
 E. L. Surgical Diagnosis Philadelphia W. B. Saunders Co. 1930)

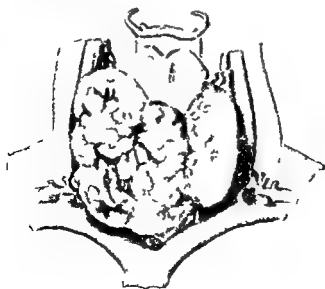


Fig. 85 Anatomical representation of carcinoma of the thyroid gland (From Pfizer
 Spectrum appearing in the J. A. M. A.)

At times a Delphian node is difficult to distinguish from a pyramidal lobe. In such situations hyperextension of the neck is helpful in determining whether the node is attached to the thyroid gland. If it is attached to the gland it will rise above the thyroid when the neck is hyperextended.

The Delphian or sub Delphian nodes (may be one or several) are the first to be exposed at the time of operation. They are usually found anterior to the larynx and the trachea. It should be remembered that this



FIG. 83 Roentgenogram showing a metastatic area in the bones of the skull from a so-called benign metastasizing adenoma of the thyroid. This lesion is considered a hybrid type of thyroid cancer because it appears benign in the original tumor but metastasizes to bone.

lymph node is often found encased in the cervical fascia in the midline just above the thyroid isthmus anterior to the lower portion of the thyroid cartilage. When this gland or glands are seen they are the first ones encountered. Examination of these nodes histologically will foretell the nature of the disease process to be found in the thyroid gland.

The Delphian node receives lymph from the upper anterior portion of the body of both lobes and from the upper poles and the isthmus. Cancer originating in any of these areas has been found to metastasize to this node or nodes. Only one exception pertains to this situation, namely, that

nongossyrous region. It appeared that the majority of cancers of the thyroid were in long standing nodular goiter.

At the present time there is no exact certitude concerning this etiological relationship. It may well be that the malignant lesions do arise in pre-existing benign adenomata. However the pathological evidence in support of this belief is not voluminous. The histological picture of a localized area in which malignant change has occurred in an otherwise benign adenoma is not a common finding. The usual picture is for an encapsulated nodule to be either entirely benign or entirely malignant throughout. Pemberton^{3, 7, 314} has reported that the proportion of cancers

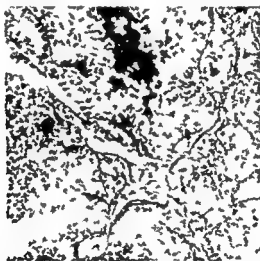


FIG. 87. Microscopic section taken from the gross specimen pictured in figure 86. The pathological picture of this section is that of adenocarcinoma.

of adenomas that arise in pre-existing goiters is far smaller at the present time than was reported in previous years.

The sequence of events concerning a benign adenoma going on to the carcinoma phase is not postulated to account for the apparent development of carcinoma in a nodular goiter. Clinical experience unfolds the fact that the less anaplastic carcinomata, especially the papillary lesions, and the great majority of malignant adenomas increase in size at a very slow pace. Our knowledge based upon statistical study clearly demonstrates that these lesions can exist for years without causing local symptoms and without giving rise to metastasis. In such patients until the metastasis spreads the lesions are considered to be clinically benign. Conversely a thyroid nodule known to be present for many years when re-

since the node which receives lymph from the larynx a carcinomatous metastasis in this node or group of nodes is not necessarily pathognomonic of cancer arising in the thyroid gland. However at operation additional examination of the thyroid will substantiate the diagnosis of thyroid cancer.



FIG. 86. Gross specimen of primary thyroid carcinoma showing the appearance of the gland on cross section. Microscopically the lesion was identified as a papilliform type of adenocarcinoma. (Rice, L. W. Histology of the thyroid gland. Medicine II. Illustrated Feb. 1949.)

Nodular Goiter and Carcinoma

The consensus among the majority of authorities appears to indicate that a pre-existing benign adenoma (especially a fetal adenoma) may be the precursor of carcinoma in the thyroid gland.^{3, 2, 3, 8, 111} The relationship between the two lesions was thought to be such that an adenoma was in fact a precancerous lesion. The evidence in support of this thought was based upon clinical experience in the majority of instances. Carcinomata were relatively common in those geographical areas where adenomatous goiter was endemic. On the other hand it was relatively uncommon in the

nongonitrous region. It appeared that the majority of cancers of the thyroid were in long standing nodular goiters.

At the present time there is no exact estimate concerning this etiological relationship. It may well be that the malignant lesions do arise in pre-existing benign adenomata. However the pathological evidence in support of this belief is not voluminous. The histological picture of a localized area in which malignant change has occurred in an otherwise benign adenoma is not a common finding. The usual picture is for an encapsulated nodule to be either entirely benign or entirely malignant throughout. Pemberton^{2, 174} has reported that the proportion of carcin-

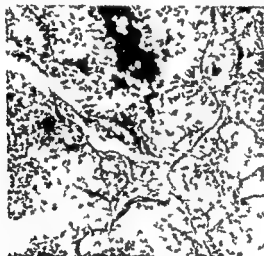


FIG. 87 Microphotomicrograph taken from the gross specimen pictured in figure 86. The pathological picture of this section is that of adenocarcinoma.

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moved at operation is found to be unrelated to carcinoma. By this it is meant that the carcinoma develops in the extranodular tissue and infiltrates or engulfs the unchanged benign nodule. It is quite probable that some carcinomata develop in pre-existing benign adenomata. The exact proportion of cases in which this occurs cannot be stated dogmatically.^{3,4} It cannot be denied that very many malignant thyroid lesions are malignant from the time that they are first revealed as nodules in the thyroid gland. For this reason the prophylactic concept of preventing the development of carcinoma by the removal of benign adenomata has both its an-

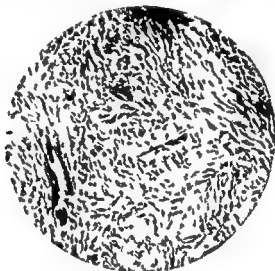


FIG. 88 Microscopic section of primary oat-cell type of thyroid carcinoma. The cells have a spindle form which easily confuses the pathologist. This type of carcinoma must especially be distinguished from fibrosarcoma and Riedel's struma. (Price L. W. Histology of the thyroid gland. Medicine Illustrated Feb 1949.)

tagonists and advocates. It should not be implied, however, that nodular goiters should be allowed to remain, since it is known that carcinoma is found often enough in nodular goiters to suggest a relationship between the two.

Unfortunately, the symptoms and signs of thyroid cancer, except for the possibility of a thyroid nodule, develop quite late in the course of the disease. A common experience is for the diagnosis to be suspected only when the lesion has metastasized or has broken through the confines of the thyroid gland. As is well known, according to the present-day concepts of malignant lesions, the interval between the development of cancer and its spread is the period during which treatment has the best chance of overcoming the progress of the disease. Unfortunately, in the majority

of patients with thyroid carcinoma this interval between development and spread is quite long. Thus it can be understood that the betterment of prognosis lies in the removal of the malignant thyroid nodule before it



FIG. 100. Roentgenogram of the lower spine (patient complained of low back pain) showing early metastasis in the lumbar vertebra from a known carcinoma of the thyroid.

has spread. This implies that nontoxic nodular goiters should be removed almost routinely.

Although the exact incidence of carcinoma in nodular goiter is not known, there is sufficient information concerning its incidence in those that have been removed surgically. This incidence in surgical material as reported in the literature varies from 4 to 8 per cent.^{2, 3, 7, 63, 365, 367, 370, 376} During the ten year period from 1938 to 1947 the incidence of carcinoma in resected nodular goiters was 4.8 per cent at the Mayo Clinic.^{3, 37} The

term nodular goiter is used at the Mayo Clinic to designate all goiters including clinically evident carcinomas that were nodular on clinical examination.

The diversity of the histological architecture of thyroid cancer and its variation in biological behavior have made pathological classification quite difficult. Many years ago there were many complex classifications of thyroid cancer so that in most instances the tabulations were not unsatisfactory. A simpler modern classification is much more preferable.



FIG. 90. Roentgenogram of clavicle demonstrating moth-eaten appearance of the inferior margins of the bone due to metastasis. The patient was a 30-year-old housewife with proven cancer of the thyroid gland.

Although renowned for their elucidation of the thyroid cancer problem its classification seems to differ among the various large clinics and groups. One of the most satisfactory classifications is that used at the Mayo Clinic. This grouping has been found adequate for the proper classification of primary malignant tumors of the thyroid gland. These lesions are grouped as follows:

- 1 Papillary adenocarcinoma
- 2 Adenocarcinoma in an adenoma (malignant adenoma)
- 3 Anaplastic adenocarcinoma
- 4 Epithelioma
- 5 Sarcoma



FIG 91 Chest roentgenogram of a female with cancer of the thyroid and pulmonary tuberculosis. This patient had a moderate swelling of the thyroid gland with tracheal compression. (Histologic section confirmed the diagnosis of thyroid cancer.) This x-ray film shows that a thoroplasty was performed. Posterior portions of the upper six ribs on the right side are missing with a moderate collapse of the thorax and incipient regeneration of the resected bones noted. Numerous healed calcific lesions are present in both upper lobes of the chest. No evidence of bone or pulmonary metastases in this chest film is recorded. This illustration is presented as a problem in differential diagnosis between pulmonary tuberculosis and pulmonary metastase.

Treatment of Thyroid Cancer

The treatment of thyroid cancer is radical. It includes surgery, high voltage radiation, or radioactive iodine. A combination of these three methods may be the usual therapeutic regimen. Hormonal therapy has

not been established as an accepted method of therapy. Of all the therapeutic modalities available one can state that the treatment of cancer of the thyroid is primarily surgical. Irradiation is of secondary importance.

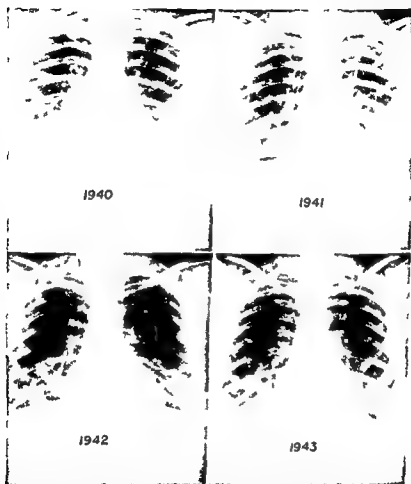


FIG. 92. Serial chest films of a 45-year-old housewife with pulmonary metastases from thyroid carcinoma. The metastases were detected in 1940. This series shows the progress of the disease with yearly interval x-ray examinations until she died in 1943. The last film shows a pleural effusion secondary to carcinomatosis.

This series of film is continued on page 195-196.

finding its greatest utility in those patients in whom all the malignant tissue cannot be resected. The extent and type of operation is governed by the extent and the type of the local spread of the carcinoma. The idea of radical removal of the primary lesion together with the tributary lymphatics en masse is not particularly applicable to the carcinomatous lesions

of the thyroid because of the anatomical relationship of this gland to the contiguous vital structures. Moreover there is much evidence to support the belief that radical dissection in the presence of certain neoplastic

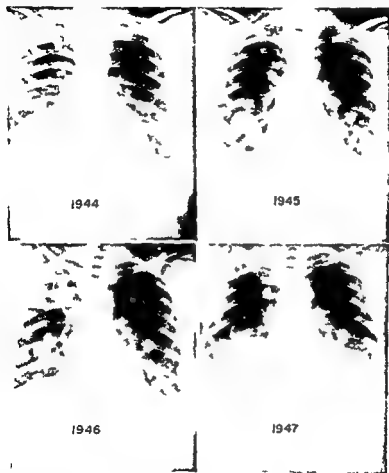


FIG. 92—continued

lesions in needle biopsies where as in other types of lesions such radical dissections are entirely useless.

Palliative Resection

In the treatment of thyroid cancer palliative surgical procedures have a most useful place. Prior to surgery it is almost impossible to determine the resectability of all but a lesion in the advanced stages. If at the time

of surgery the lesion proves to be inoperable locally, the surgeon should, nevertheless try to remove as much of the malignant tissue as possible. The tissue that remains can be treated by radiation, by the implantation of radon seeds etc. Moreover postoperative external irradiation is usually

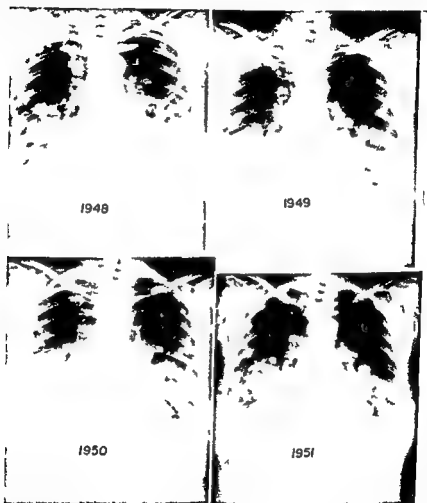


FIG 92—continued

more effective after the resection of a large portion of the malignant tissue since the treatment can then be limited to smaller areas.

In some patients with advanced carcinoma the surgeon is restricted as to the amount of resection. Under this circumstance he may only be able to perform a biopsy and/or establish an airway. It is mandatory for the surgeon however, to attempt to free the trachea from the carcinomatous mass at the time of surgical exploration. The establishment and main

tenance of an airway is among the principal end result of palliative operative procedures.

Tracheotomy may be a life saving procedure in patients with thyroid cancer. For this reason it should be considered in any case in which an extensive dissection is performed in the area of the larynx and the trachea. Tracheotomy should be performed especially where large masses of malignant tissue cannot be removed and must remain in the neck. It is also advisable to perform a tracheotomy when irradiation is planned following surgery. The optimum time for performing a tracheotomy is when the patient is in the operating room for the original palliative procedure. For it is at this time that it is safer and easier to perform. As the disease progresses a patient with thyroid cancer will develop tracheal obstruction.



FIG 92—continued

When this stage is reached any attempt to find and to open the trachea in the presence of recurring carcinoma is not only extremely dangerous but is technically most difficult. On occasion it may be necessary to pass a bronchoscope to maintain an airway while the surgeon tries to dissect away carcinomatous tissue to find the distorted and displaced trachea for a tracheotomy.

On occasion the question of performing a gastrostomy is raised. It is rarely necessary to perform this procedure in patients with thyroid carcinoma because unfortunately the patient dies before a complete esophageal obstruction results.

Radiation Therapy

External Irradiation Although external irradiation has been used for many years in the treatment of thyroid cancer it is difficult to find un-

of surgery the lesion proves to be inoperable locally the surgeon should, nevertheless try to remove as much of the malignant tissue as possible. The tissue that remains can be treated by radiation, by the implantation of radon seeds, etc. Moreover postoperative external irradiation is usually

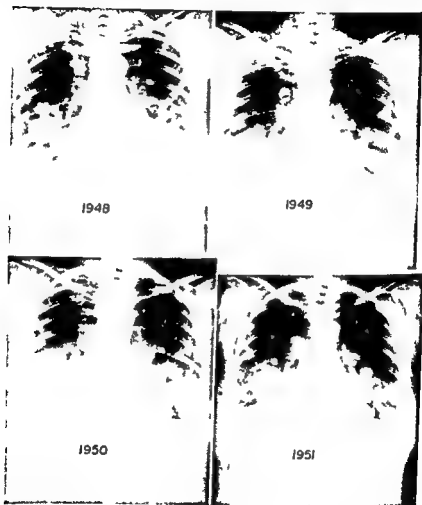


FIG 9^c—continued

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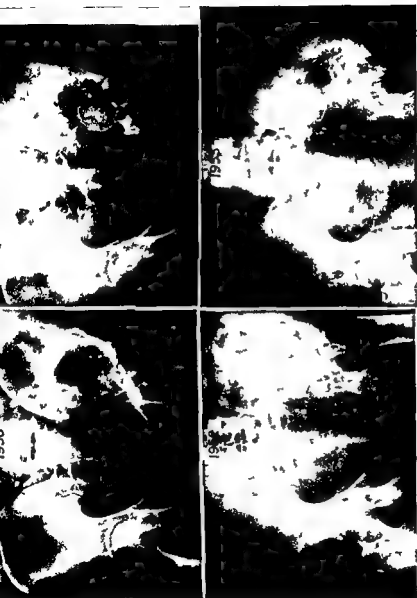


FIG 3 Serial roentgenograms showing metastases to the left pelvis arising from thyroid carcinoma. The patient was seen for the first time in 1941 and died in 1953. This series demonstrates the progression of the lesion from venous extension excepting 1946 and 1953. In 1944 the metastasis was found in the left ilium. A gradual inferior extension of the disease noted to involve the pubis and ischial bones. Clinically the advancement of the disease, the head of the femur is seen to erode through the acetabulum. Clinically the patient became a grid mal cripple as the process advanced. She finally was completely bedridden until her death.



animity of opinion is to its effectiveness. Pemberton has collected statistical evidence indicating that the survival rates are somewhat better in those patients who have had resection plus irradiation than in those who had surgical resection alone. It was not so long ago that most radiologists believed that irradiation not only decreased the rate of thyroid cancer growth but actually diminished the size of the lesions. Today there is less certainty as to the efficacy of irradiation. The improvement following



FIG 94 The long incision to be made for the radical removal of the thyroid lobe for cancer in the gland. With this incision it is practicable to remove the sternocleidomastoid muscle, the internal jugular vein, the thyroid veins and lymph nodes.

irradiation is usually temporary, limited and often merely palliative. Some authorities do not even recommend irradiation postoperatively in those cases in which all known carcinomatous tissue has been removed. The author's personal preference is to employ combined surgery and irradiation in patients with thyroid cancer.

Of course, certainly, in those cases in which the primary lesion cannot be removed completely, external irradiation is advisable. The end results of irradiation treatment for papillary lesions and malignant adenomas are most difficult to evaluate. As a general statement it can be said that if a

neoplastic lesion of the thyroid resembles lymphomatoid lesions the response to irradiation is better than in the e tumors which demonstrate larger cells, giant cells or cells resembling fibro carcinoma. This latter group is usually not affected by external irradiation.

Interstitial Irradiation In order to treat small masses of nonresectable

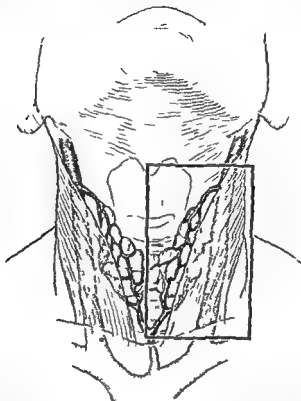


FIG 96 Diagram showing the block of tissue to be removed in patients with carcinoma of the thyroid gland. This block includes the sternocleidomastoid muscle, the internal jugular vein with all of its tributaries entering the thyroid gland, all the lymph nodes and all the thyroid tissue bilaterally. (Lahey, F. H. and Fierman, B. J. Lateral aberrant thyroid. *Surg. Gynec. & Obs.* 82: 705-711, 1946.)

carcinomata one may employ radium needles or radon seeds. This method of therapy is not offered as a curative process. However, prolonged survival after treatment with radium needles or radon seeds can be attributed to a slower progression of the lesion. Irradiation of metastatic lesions not in the neck region is a useless procedure.

Radioactive Iodine A new modality of therapy is now available for the treatment of thyroid carcinoma in radioactive iodine. This isotope has a limited though definite place in the treatment of certain cases of thyroid

■ carcinoma It is not the method of choice for the treatment of the lesions which can be removed surgically. Radioactive iodine is an available adjunct in the management of inoperable extensions or metastatic growths. Its efficacy depends upon the ability of the malignant tissue to concentrate an adequate amount of radioactive iodine. Unfortunately, some malignant thyroid lesions will not concentrate an adequate amount. It may be necessary to stimulate this function before treatment is possible. In any case the thyroid gland must be removed totally or destroyed by means of radioactive iodine before the malignant metastatic tissue can be treated.

For this reason certain lesions cannot be treated with the isotope because they cannot be stimulated to concentrate radioactive iodine. Among these lesions which fall into this category are

- 1 All anaplastic lesions
- 2 Hurthle cell type of malignant adenoma
- 3 Papillary lesions with no follicular component
- 4 Malignant adenomas composed of solid sheets of cells without follicles or colloid

On the other hand, some types of thyroid carcinoma can be treated by isotopic irradiation and with such good possibilities that attempts should be made to use radioactive iodine. Stated in a different way, there appears to be a definite correlation between the presence of follicles (histologically) and the function of concentrating iodine. The probability that a thyroid carcinoma can be treated satisfactorily with radioactive iodine can at times be prognosticated therefore from the cytoarchitecture of the lesion as revealed by the microscope.

A determination by surgical exploration that the lesion is either resectable or not resectable is therefore the initial step in the management of a thyroid carcinoma patient. At the time of operation all or as much malignant tissue as possible should be removed. If the pathological picture of the removed thyroid cancer is such that there is a possibility of stimulating radioactive iodine uptake, then total thyroidectomy should be performed. On the other hand, if the lesion is not operable because of extension it may still be possible to remove all or almost all of the uninvolved thyroid. In any event the surgeon should remove as much of the thyroid gland as possible. When surgical removal is not possible, the thyroid gland must be destroyed by radioactive iodine. Surgical removal is far superior to destruction by radioactive iodine, however. Although the exact reactions are not clear, it must be recalled that surgical removal extirpates all thyroid tissue, whereas radioactive iodine apparently destroys the follicular elements leaving behind a cadaveric gland which may still possess a hormonal function.

Following the destruction of the thyroid gland, the patient is given an

antithyroid drug which does not contain iodide. The drug may be administered for 3 months or more. The object in view is to produce complete myxedema. The presence of myxedema inhibits the secretion of the thyroid stimulating hormone which acts to stimulate the iodine trapping function of the lesion to be treated. When the myxedema is clinically in evidence the administration of the antithyroid drug is discontinued. Forty-eight hours later the iodine concentrating function of the metastatic lesion is determined by means of a tracer dose of radioactive iodine. An ade-

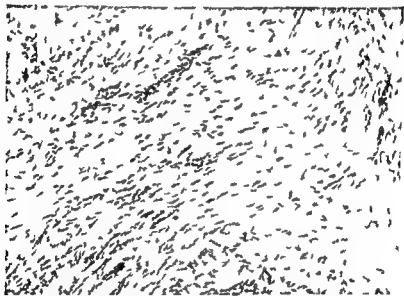


FIG 97 Photomicrograph showing complete destruction of thyroid tissue with radioactive iodine. The parenchyma has been replaced by fibrous tissue. This type of destruction of malignant tissue is possible if the lesion can be made to concentrate a sufficient amount of radioactive iodine (Pemberton J and Black B M. Cancer of the thyroid. American Cancer Society Bulletin 1954)

quate uptake is evaluated by the Geiger counter and urinary excretion is determined. If the results are satisfactory a massive dose of radioactive iodine is then given. This procedure is continued until there is no longer any uptake or until the patient has received the maximum dose possible. The administration of radioactive iodine is an individualized problem. The duration of treatment and the amount to be administered is determined by the radiologist in conjunction with a physician. The ultimate results of treatment by radioactive iodine cannot be accurately evaluated at this time. It is known however that many metastatic lesions have been destroyed and that prolonged survival without evidence of the disease

can be attributed to the isotope. In many cases treatment is unsuccessful because the metastatic lesions cannot concentrate iodine.

Many years ago the distinguished Italian surgeon R. Allemandi read an interesting paper before the Clinical Congress of the American College of Surgeons (Montreal, October, 1926). The title of this discourse was

Thyroid and Parathyroid Bone Tumors without Primary Lesion of the Thyroid Gland. At this lecture he reported a case in which he believed that carcinoma developed in secondary thyroid or embryonal aberrations located in osseous tissue. He postulated his hypothesis on the type of bone lesion without primary thyroid carcinoma in the neck. To quote Prof. Dr. Allemandi: "I do not wish to examine further the etiological hypothesis but rather to consider the question of prognosis and invading osseous thyroid tumors with osseous metastases and every evidence of malignancy but without a primary malignant tumor of the thyroid gland. Do they really exist or are the related cases simply errors resulting from excessive haste in reporting the case or incomplete study of patient?"

It is difficult to believe that primary thyroid cancer is found in bone. A more logical hypothesis would be that the bone lesions are metastatic lesions originating in the thyroid gland itself. Perhaps the primary lesion went undetected until the metastases occurred. Surgical removal of the thyroid gland in the case reported may have identified thyroid carcinoma in the neck.

Thyropar following Thyroidectomy for Cancer

The use of Thyropar (T-H) following thyroidectomy for carcinoma has been advocated by some investigator.⁴

Thyropar may be used in the management of postoperative thyroidectomies for carcinoma (1) to indicate the need of further I^{131} therapy and (2) to increase the uptake of therapeutic dose of I^{131} .

In one method of management if there is more than 30 per cent uptake of a tracer I^{131} dose after 8 daily 10 L. doses of Thyropar then a therapeutic dose of I^{131} is indicated. Fewer doses of T-H will also increase the uptake of I^{131} . If T-H does not cause this increase in the I^{131} uptake the patient probably does not require I^{131} therapy at that time. Later follow up with the same procedure at 4-6 month interval may indicate that further I^{131} therapy is needed.

The initial T-H is administered after a tracer I^{131} dose is given about 12-18 hours after the last T-H dose. I^{131} uptake is determined 24 hours after the tracer dose of I^{131} .

This method of therapy entails the use of desiccated thyroid in the postoperative patient in order to maintain a euthyroid state. Endogenous

TSH production is thereby depressed. The use of thyroid medication does not interfere with the effect of the exogenously administered TSH.

Dosage and Administration Thytropar is administered by intramuscular or subcutaneous injection after dissolving the powder in 2 to 3 cc of physiologic saline solution. The following dosage suggestions are based on investigative data and clinical experience.

- 1 In the differential diagnosis of primary thyroid from pituitary myxedema. A single dose of 10 USP units intramuscularly will effect a consistent elevation of the serum protein bound iodine level in pituitary myxedema but will fail to do so in primary thyroid myxedema.
- 2 In functioning metastatic thyroid carcinoma. A single intramuscular dose of 10 USP units effects a significant increase in the thyroid uptake of radioactive iodine (I^{131}).
- 3 In acute thyroiditis. 10 USP units intramuscularly daily for 5 to 6 days.

Caution If pituitary myxedema is suspected Thytropar should be administered with the same care that would be exercised in using thyroid extract to prevent precipitation of adrenal cortical insufficiency. It is supplied as a sterile lyophilized powder in single 6 cc vials containing 10 USP units of thyrotropic activity per vial.

Thytropar is commercially prepared thyroid stimulating hormone (TSH). It is a highly purified lyophilized thyrotropic principle of bovine anterior pituitary glands. In a dry state it is stable indefinitely at room temperature. It dissolves readily in physiologic saline solution and when refrigerated retains its potency in solution for at least 4 days.

In addition to its being used to increase the concentration of therapeutic doses of radioactive iodine within metastatic thyroid carcinoma, it may be employed as follows:

- 1 As an aid in the differential diagnosis between primary thyroid myxedema and pituitary myxedema.
- 2 For the symptomatic relief and ancillary treatment in acute thyroiditis (acute diffuse thyroiditis, acute nonsuppurative thyroiditis, subacute thyroiditis).

Addenda

Our present knowledge of cancer is changing from the concepts held not too many years ago. One aspect of the cancer problem, however, has not changed since the thundering herd days of Virchow, namely, that carcinoma can be eliminated by the surgeon himself. More specifically, papillary carcinoma of the thyroid gland if treated gently by the surgeon

may not give the patient too much trouble. However if a papillary carcinoma is unbridled (if it is squeezed or broken) then it can become a mechanically induced metastatic disease. When a papillary carcinoma of the thyroid has been disturbed and/or disseminated via the surgical procedure it may become so erratic that no surgical means, however radical can be of any assistance.

The best means of handling a patient with this disease is often a highly speculative one if the reader takes seriously the various reports in the world literature. There are very few authorities who are in accord with one another and it behooves us to know how and why to do the procedure of choice. The lack of uniformity of opinion has resulted in the type of confusion that leaves the general surgeon open to both criticism and malpractice liability. For this reason a definite plan of treatment must be established and accepted for better or for nor.

The consensus seems to be that when discussing thyroid cancer the following factors should be our guide:

- 1 In almost all cancers of the thyroid gland (excepting rare tumors) the zone of metastasis is central and medial. The most frequently involved nodes therefore are those of the superior mediastinum and the lymphatic chain found behind the thyroid gland and along the trachea and esophagus. Since these nodes lie in close proximity to most vital structures they must be dissected meticulously and cannot be removed in the en bloc dissection advocated by many specialists in this field. (This thought must be considered seriously when a radical neck dissection is advocated.) By the same reasoning it is not logical to insist upon an en bloc dissection of the secondarily involved lymph nodes.

- 2 The cause of death in patients with a papillary adenocarcinoma is not found in the metastases but rather in the compression of vital structures in the neck secondary to medial and central metastases. Thus the central area of the neck is the battle ground where victory or defeat is to be found.

- 3 Radical neck surgery with removal of the sternocleidomastoid muscle in a young girl should not be advocated too strongly because this muscle is very important to the cosmetic appearance of the young girl and the Courts of Law do not uphold this procedure since there are so many well regarded authorities who do not advocate radical surgery of this type for papillary adenocarcinoma. In addition the radical surgery often injures the eleventh nerve and this may result in additional complications such as a shoulder drop and secondary arthritic changes.

- 4 The changing concept of the biological activity of thyroid cancer has made us wonder if papillary adenocarcinoma of the thyroid gland can be treated satisfactorily by means of a noncontinuous dissection of the

neck. The involved glands with preservation of the muscular elements of the neck will preserve its anatomical appearance.^{6,4}

5 It has been found that many low grade tumors of the thyroid (with malignant changes) may regress if a sufficient quantity of thyroid extract is given to suppress the thyroid stimulating hormone of the pituitary gland.

6 Thought must be given to the fact that a thyroid cancer may contain two or more elements of different tumors. They are similar to mixed tumors. This is especially true in patients under 35 years of age. The most commonly seen mixture in tumors of the thyroid is follicular carcinoma with papillary adenocarcinoma. The biological activity of these tumors approximates the papillary type although histologically the appearance resembles the follicular carcinoma much more architecturally.

7 The prognosis in patient with papillary adenocarcinoma is good, some patients having survived 15 and some 20 years. The routine use of desiccated thyroid (3 gr daily) may be a factor in the favorable prognosis. Crile believes that papillary adenocarcinoma of the thyroid gland is dependent upon the thyrotropic hormone and that in many cases it is a reversible disease that resembles endometriosis more closely than autonomous cancer. He also believes that a surgeon should think carefully before advocating a mutilating neck dissection for a disease that can be as well controlled by a less radical procedure that preserves the function and contour of the neck.^{6,4}

Conclusions on Treatment

1 Given a patient with hyperthyroidism (without evidence of cancer) three methods of therapy are available. These methods are radioactive iodine, antithyroid drugs or surgery.

2 Radioactive iodine therapy is the simplest method for the patient. Its greatest disadvantage is the possibility of late carcinogenesis.

3 Antithyroid drug therapy is simple for the patient. Its greatest disadvantages are prolonged administration of the drug, a high recurrence rate when the drug is stopped, and the danger of carcinogenesis.

4 Surgery is still the time tried standard of bringing prompt relief. Moreover, surgery enables the pathologist to identify properly the underlying disease.

5 The rapidly falling morbidity and mortality following thyroidectomy eliminate the objections to surgery in a great measure. Surgery permits the establishment of the presence of cancer and enables radical therapy to be instituted immediately.

6 Thyroid cancer is treated by surgery, radiation therapy, and/or radioactive iodine. In some cases all three methods may be employed.

7 Surgery is the oldest and most commonly used therapeutic method.

High voltage radiation is an ancillary supplement and is palliative in the undifferentiated cancers. Radioactive iodine is most effective in two forms of cancer: (a) The differentiated adenocarcinoma. (b) The differentiated metastasizing adenoma. (In the original lesion it often appears benign.)

Persistent and Recurrent Thyroid Diseases

On occasion a patient is subjected to active surgical therapy for the treatment of certain pathologic condition of the thyroid gland without obtaining the desired effect. Although the therapeutic method may have been well planned and executed with dexterity the end result may not be satisfactory as the surgeon and the patient anticipated and desired. If the failure to secure the desired result is manifested immediately after the cessation of treatment the term persistent may be used to describe the clinical picture. If on the other hand the symptoms or signs return any time after the immediate postoperative period it is proper to label that state as recurrent thyroid disease.

The persistence or recurrence of symptoms is most frequently seen in primary hyperthyroidism and cancer. This distressing state may occur even though the patient has been subjected to what apparently was considered to be an adequate thyroidectomy. It has been the sad experience of many surgeons to find that a persistence and even an aggravation of toxic symptoms has occurred following surgery. This type of patient is best treated by postoperative radioactive iodine with repeated surgery reserved for those individuals who develop thyroid nodules in the neck. Any nodule present or recurrent after thyroidectomy should be removed surgically.

In those instances in which a patient has had a total or subtotal thyroidectomy for adenomatous goiter a recurrence of a mass in the neck due to thyroid tissue should incur additional surgical removal. In simple adenoma recurrence may be in reality a persistence and growth of a previous small—even microscopic—adenoma which was overlooked at the time of surgery. For this reason when a simple unilateral adenoma is found the opposite lobe should be removed as well as the involved lobe even though no adenoma is visible or palpable. It has also been the sad experience of many surgeons to see a large adenomatous goiter extend subternally with tracheal compression within 2 years after hemithyroidectomy for an apparently solitary adenoma.

Recurrence of symptoms in patients operated upon for thyroiditis is not usual. If the initial symptom was tracheal compression and adequate surgery was performed it is indeed a rare occasion for the surgeon to reoperate. Prophylaxis against a recurrence of compression symptoms in

neck. The involved glands with preservation of the muscular elements of the neck will preserve its anatomical appearance.^{7, 8}

5 It has been found that in many low grade tumors of the thyroid (with malignant changes) may regress if a sufficient quantity of thyroid extract is given to suppress the thyroid stimulating hormone of the pituitary gland.

6 Thought must be given to the fact that a thyroid cancer may contain two or more elements of different tumor. The elements are similar to mixed tumors. This is especially true in patients under 30 years of age. The most commonly seen mixture in tumors of the thyroid is follicular carcinoma with papillary adenocarcinoma. The biological activity of the elements approximates the papillary type although histologically, the appearance resembles the follicular carcinoma much more architecturally.

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7 Surgery is the oldest and most commonly used therapeutic method.

14

Ectopic Thyroid and Other Anomalies

BEING A highly vascular endocrine gland with powerful physiological activity, the thyroid may be the victim of embryological disturbances similar to other ductless glands of analogous potentialities

Ectopic thyroid tissue may be explained on the basis of one or both of the following^{1 2}

- 1 Thyroid anlage may come to rest anywhere along the normal thyroid invagination during embryonic development. This invaginating pathway extends from the tongue to the mediastinum. Hence the presence of lingual thyroid, thyroglossal cysts and intrathoracic goiters.
- 2 Microscopic cellular thyroid anlagen may be scattered or displaced to distant cell structures of similar physiologic destiny like another endocrine gland. Thus thyroid tissue may be found in an ovary or may be part of a teratoma wherever a teratoma may occur.

Irrespective of its location thyroid tissue may undergo any physiologic change that is possible in a thyroid gland that is found in its normal anatomic location. In other words the anomalous or ectopic thyroid may become a goiter in any of the varieties that normally placed thyroids give rise to.^{3 4} Moreover it is usually only when the ectopic or anomalous thyroid becomes pathologic that it is discovered. It should be remembered that ectopic thyroid tissue may be the only thyroid in the patient and if it is removed myxedema may occur.

The varieties of thyroid anomalies recorded are

- 1 Ectopic location of parenchyma
 - a lingual goiters
 - b Intrathoracic goiter
 - c goiter plongeant
- 2 Teratomata
 - a ovarian (struma ovarii)
- 3 Thyroglossal duct anomalies
 - a cysts
 - b sinuses

patients with struma lymphomatosa or Riedel's struma can be reasonably assured if the trachea is cleansed completely of thyroid tissue. When it is not feasible to leave the trachea free of thyroid tissue then the next best procedure is to make certain that there is no contiguity of thyroid tissue between the thyroid remnants. If the right remnant touches the left remnant, then there is a future possibility that there will be a bridge of tissue across the trachea which at some future time may be the nidus for recurrent thyroid growth and tracheal compression.

Recurrence in thyroid cancer is a problem in itself. Since cancer in the thyroid has various degrees of malignancy (depending upon its pathologic type and biological activity) it responds to therapy in a fashion corresponding to its type as described histologically and biologically. The use of radical surgery, radiation therapy and radioactive iodine have lowered the mortality and have given a more favorable prognosis to patients victimized by thyroid cancer.

answered in this way. It may be analogous to the teatiele and termed an undescended thyroid.¹³¹ In this way too thyroids have been found at the base of the tongue between the foramen cecum and the hyoid bone. They may project into the pharynx from the dorsum of the tongue or actually be within or beneath the tongue. A useful point has been emphasized in reference to lingual goiter. The point in question is that if no thyroid is the mass whatever can be palpated in the neck, it is probable that the lingual

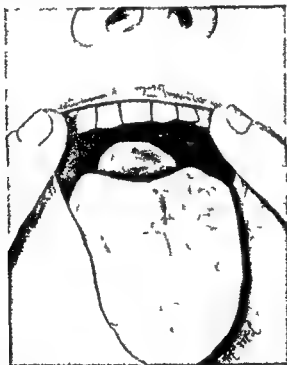


FIG. 99 Lingual goiter (Means J. H. Thyroid and its Diseases Philadelphia J. B. Lippincott 1937)

thyroid is an ectopic gland and not merely an accessory gland, i.e. it is the patient's only thyroid tissue.¹³⁴

When the thyroid descends too far and resides within the thorax, it is a true pathologic process and not an anomaly. As the term intrathoracic or substernal implies, it indicates that the lower pole or poles of the thyroid or a nodule of the gland has passed beyond the level of the upper border of the sternum. More specifically, the term substernal could be employed for those goiters with the greatest diameter above the sternum and intrathoracic for those in which it is below the sternum. Means has sug-

During normal embryonic development the thyroglossal tract from the foramen caecum to the pyramidal lobe of the normal thyroid usually dis-

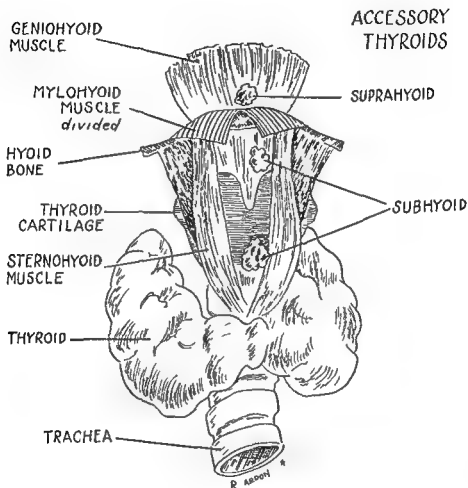


FIG 98 Sites where ectopic thyroid tissue may be found. Tissue of this type is usually discovered in the cervical midline arising from misplaced anlage. The term accessory thyroid has been used to identify this type of tissue. The name aberrant thyroid tissue has been used also to indicate the same thing. It is more accurate to employ the term accessory thyroid. The above depicts two ectopic thyroid tissue sites represented in the suprahyoid and the subhyoid area.

appears by midfetal life. In its movements, however, it may leave behind small segments of tissue which may develop into accessory thyroids. There may even be a complete failure of the entire thyroid structure to reach its normal destination in the pretracheal region. The lingual thyroid may be

of years it grows quite large and heavy. The weight of the goiter becomes sufficiently ponderous enough to actually drop into the chest and come to rest on the diaphragm. This displacement may be relatively rapid in its course as when a goiter starts in the upper mediastinum and gradually finds its

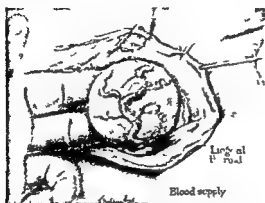


FIG 102 Further dissection enables the surgeon to elevate the tumor for removal after the tongue has been displaced into the operative site (Ward G E Cantrell J R and Allan W B Surgical treatment of lingual thyroid Ann Surg 139 May 1954)



FIG 103 After the lingual thyroid has been removed a defect remains in the tongue. The wound is closed and a temporary drain is usually employed (Ward G E Cantrell J R and Allan W B Surgical treatment of lingual thyroid Ann Surg 139 May 1954)

way into the lower thorax. If the process is an inordinately slow one and the transposition is gradual the examiner may speak of this as a migrating goiter.

Teratomata are true embryologic anomalies. In some teratomata (in lieu of the displacement of the thyroid anlage or a portion of it) there is a growth of thyroid tissue together with other tissues. The ovaries are the commonest location for this symbiotic growth. In a thyroid tumor of the ovary (struma ovarii) it appears as if the thyroid tissue has developed

gested the use of 'incomplete intrathoracic' for the first and "complete intrathoracic" for the second.¹³¹ An intrathoracic goiter may be found years after the removal of a cervical thyroid. Intrathoracic goiters are surgically important because they may produce mechanical pressure



Fig 100 Lingual thyroid as seen through the mouth with the tongue pulled as far forward as possible (Ward G F, Cantrell J R and Allan W B. Surgical treatment of lingual thyroid. *Ann Surg* 139 May 1954)

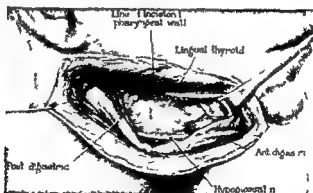


Fig 101 Surgical approach to lingual thyroid tumors. This exposure of the lateral pharyngeal wall shows the tumor beneath the mucous membrane. The pharyngeal incision is indicated by the dotted line (Ward G E, Cantrell J R and Allan W B. Surgical treatment of lingual thyroid. *Ann Surg* 139 May 1951)

changes like other mediastinal tumors. Lingual goiters, on the other hand, are surgical curiosities and removal is indicated because of inconvenience to the patient rather than for obstructive symptoms.

Goiter plongeant (diving goiter) is one that has plunged into the thorax and rests within that cavity in a dependent location.¹³¹ This type of goiter usually finds its origin in the neck or upper mediastinum. Over a period

of the ovary. That genuine thyroid tissue is present has been demonstrated by chemical determinations of the iodine content as well as by histological study.¹²⁸ As a matter of record there are 4 cases reported in which a thyroid tumor of the ovary was actively functioning causing hyperthyroid signs and symptoms.¹²⁹⁻¹³² While thyroid tumors of the ovary are usually benign cases have been reported in which malignancy was present with metastasis and eventual death.¹³³

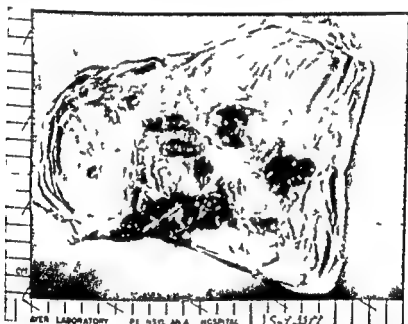


FIG 10a Surgical specimen of ovary demonstrating the gross appearance of truma ovarii. The central black bulging gelatinous areas represent the thyroid elements (Courtesy A. R. Crane, Ayer Clinical Laboratory of Henshaw Hospital Philadelphia.)

Thyroglossal duct anomalies do not involve gland parenchyma. Retention cysts due to a dragging down of pharyngeal tissue during the growth of the thyroglossal tract are occasionally observed. A cyst of this type may communicate with the pharynx at the foramen cecum via a fistulous remnant of the duct. True external thyroglossal fistulae (those having an embryonic origin) do not occur since the thyroglossal tract at no time communicates with the skin of the neck. Pathologic external sinuses may be formed by the external rupture of a thyroglossal cyst or when a surgical incision is made into it.¹³⁴

Thyroglossal cysts appear most often during infancy and childhood

at the expense of the other elements in the ovary.¹³³ While the histologic picture leaves little doubt as to the thyroid nature of the tumor tissue, one



FIG. 104. Goiter plongeant (diving goiter). The mass in the right chest (larger than the heart) is the goiter. The right lower lobe of the lung reveals some atelectasis. Goiter plongeant is a term applied to goiters which have plunged into the thorax. (Means J. H. *Thyroid and its Diseases*. Philadelphia: J. B. Lippincott, 1937.)

may be misled by the pseudothyroid appearance. At times this is seen as

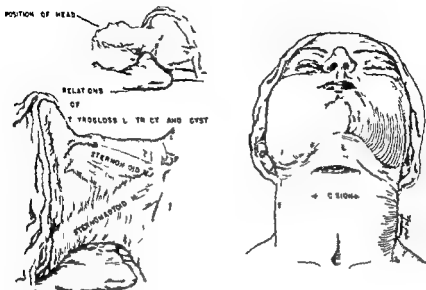


FIG. 108 Illustrations of position of head and type of incision for removal of thyroglossal tract abnormalities in the upper neck. A similar type of incision is used for thyroglossal abnormalities in the lower part of the neck (Pedrawn from St. trunk) (Ward G. E. Hendrick J. W. and Chambers R. C. Thyroglossal tract abnormalities Surg. Gynec. & Obst. 29: 72, 1919)



FIG. 109 Endotracheal tube in place. Assistant's finger in the mouth forces base of tongue and foramen upward, forcing out stalk of tract (Modified and redrawn from St. trunk) (Ward G. E. Hendrick J. W. and Chambers R. C. Thyroglossal tract abnormalities Surg. Gynec. & Obst. 29: 72, 1919)

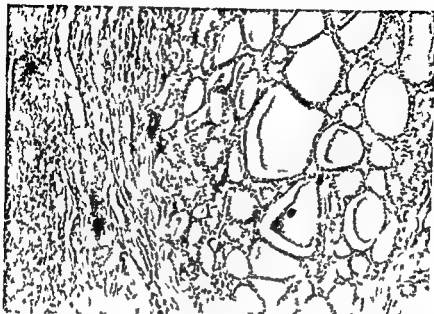


FIG 106 High power view of thyroid tumor of the ovary (struma ovarii) demonstrating thyroid tissue on the right and non-specific ovarian tissue on the left (Picture No 88346 Courtesy of Armed Forces Institute of Pathology Washington D C)



FIG 107 Sagittal view showing the locations of thyroglossal cysts (From Pfizer Spectrum appearing in the J A M A)

Infrequently they are seen initially during adult life. They may become infected and drain pus via a fistulous opening at the foramen cecum or rupture externally. As previously stated they may be incised surgically. When any of the conditions occur a draining sinus results. Intermittent healing with reopening without permanent spontaneous healing is the usual trilogy of events. In chronic cases the sinus tract may be palpated as a

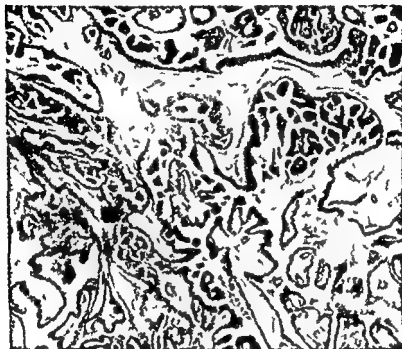


FIG. 117. Histological section ($\times 40$) of the operative specimen removed from the patient in figure 111. The cellular architecture is that of papillary medullary carcinoma as seen in some thyroid tumor. (Byrne J. J. Carcinomas of the thyroid. *Boston Med Quart* 31, No. 3, 1900.)

fibrous cord extending from the external opening to the level of the hyoid bone. The sinus opening is usually found somewhere between the thyroid isthmus and the hyoid bone along the midline of the neck.

Treatment of this condition consists of a complete dissection and removal of the entire sinus and cyst. The tract must be followed as far as it goes in the direction of the foramen cecum. It is usually necessary to remove a segment of the hyoid bone in order to insure a cure. If any thyroid gland tract remains a recurrence is inevitable.

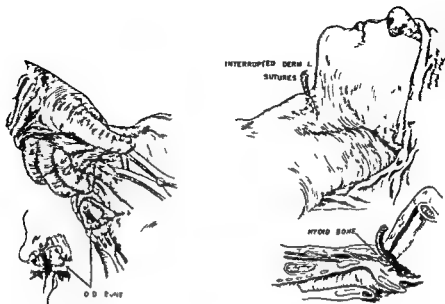


FIG 110 Method of suturing the hyoid bone and closing the wound Drain inserted (Redrawn from St trunk) (Ward G E Hendrick J W and Chambers R G Thyroglossal tract abnormalities Surg Gynec & Obst 89 72 1949)



FIG 111 Anterior and lateral views of a patient with a thyroglossal cyst in which carcinomatous change occurred (Byrne J J Carcinoma in a thyroglossal cyst Boston Med Quart 3 No 3 1960)

Infrequently they are seen initially during adult life. They may become infected and drain pus via a fistulous opening at the foramen cecum or rupture externally. As previously stated they may be incised surgically. When any of the above situations occur a draining sinus results. Intermittent healing with reopening without permanent spontaneous healing is the usual trilogy of events. In chronic cases the sinus tract may be palpated as a

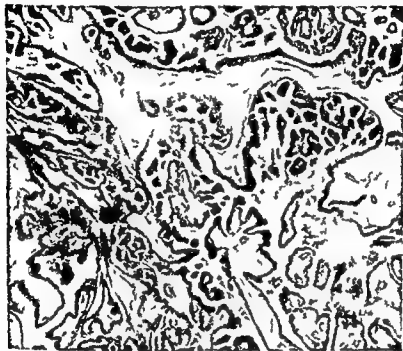


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Carcinoma in Chronic Thyroglossal Anomalies

The development of carcinomatous changes in a thyroglossal cyst or sinus is an unusual complication. However this pathological change does occur and is often unsuspected until the pathologist's report is read. When this complication is the result of a chronic sinus or cyst the microscopic picture of the neoplasm is quite similar to that seen in the thyroid gland itself. The most common lesion is papillary adenocarcinoma. Carcinoma in a thyroglossal anomaly should be treated similarly to carcinoma arising in the thyroid gland of similar histological appearance.

Exophthalmos

A MOST DISTRESSING complication of hyperthyroidism may be severe exophthalmos (also termed exophthalmia). This may be either unilateral or bilateral, stationary or progressive. Often it becomes so marked that specific measures are taken to prevent the loss of vision. Fortunately the use of modern methods for treatment has resulted in a lessening of the severity of exophthalmos.

Another good reason for the reduced incidence of exophthalmos is the exophthalmometer. Before its advent surgeons used to label as exophthalmos any retraction of the eyelid or widening of the palpebral fissure (Dalrymple sign). Measuring with the exophthalmometer often indicates that exophthalmos is not yet present.

The following discussion on exophthalmos is adapted from an article by the late André Crotti, one of America's outstanding pioneers in the thyroid surgery.¹¹

Exophthalmos in Thyrotoxicosis

In the majority of instances there seems to be a direct relation between the severity of thyrotoxicosis and the degree of exophthalmos. The latter increases with the thyrotoxic syndrome or subsides with the disappearance of the toxic goiter. Hence the conclusion that exophthalmos is of thyroid origin. This point of view is corroborated by the fact that, as has been proved experimentally and clinically, forced feeding of desiccated thyroid gland does produce the thyrotoxic syndrome as well as the exophthalmos associated with thyrotoxicosis. It is further substantiated clinically by the results obtained with thyroidectomy.

However in recent years the trend has been to regard the pituitary gland as the primary cause for thyrotoxicosis and its concomitant exophthalmos. The claim is made that an excess of thyrotropic hormone of the anterior pituitary in the blood acts as the primary initiator and influences hyperfunction thus producing both the thyrotoxic syndrome and the exophthalmos.

There seems to be no question that there is an intimate functional relation between the thyroid and the pituitary in producing the thyrotoxic

syndrome. What the intimate mechanism is, no one knows. The excess of thyrotropic hormone does not seem to be an adequate explanation however since there are diseases in which the thyrotropic hormone is present in abundance such as acromegaly or spontaneous myxedema where no thyrotoxic syndrome or exophthalmos appears.

A frequent characteristic of thyrotoxic exophthalmos is the absence of mydriasis. This sign is quite interesting. Stimulation of the cervical sympathetic nerve produces exophthalmos with mydriasis. This is to be expected since resection of the cervical sympathetic nerve will produce enophthalmos and miosis.

In adenoma of the anterior pituitary, acromegaly and the Cushing syndrome, exophthalmos is observed long before the other clinical symptoms occur. Here also mydriasis is absent. This absence of mydriasis would make it appear that thyrotoxic exophthalmos and pituitary exophthalmos are the same.

One should remember that exophthalmos experimentally produced with the thyrotropic hormone is by no means constant and that the effect upon the thyroid is fleeting and soon ceases to be active no matter how long it is administered. On the other hand it would appear that thyrotropic hormone does not produce exophthalmos by activating the thyroid gland since exophthalmos is best obtained in thyroidectomized animals.

Recently Doryns and Wilson³⁴ reported that they had separated two substances in the pituitary secretion. One of the substances is capable of producing hyperplasia in the thyroid gland. The other can produce exophthalmos. A few micrograms of the second substance can produce exophthalmos in the Atlantic minnow within 3 to 8 hours. Some patients with severe exophthalmos have been studied and it was found that they have this substance in their blood sera.

Another significant fact is that exophthalmos is observed only with thyrotoxic goiter and not with simple nontoxic goiter. Furthermore, post-operative progressive exophthalmos is observed only after thyroidectomy for thyrotoxic goiter and never after thyroidectomy for simple nontoxic goiter, no matter how extensive the latter operation has been. Now if thyroid insufficiency must be present to allow the thyrotropic hormone to produce exophthalmos, why is exophthalmos not present in cases of post-operative myxedema following thyroidectomy for simple nontoxic goiter? That exophthalmos can be explained on the basis of disturbed autonomic control is perhaps probable, but the role of the sympathetic system is not clearly understood. It must be admitted that the intimate mechanism responsible for the production of exophthalmos is still unknown.

However, it is not difficult to understand the physical mechanism that induces eyes to bulge. It is known that the retrobulbar tissues, fat and

muscle undergo tropic disturbances and become edematous and that leukocytic infiltration takes place. On the other hand the orbital space is a pyramid widely opened outside and sharply pointed inside. The walls of the pyramid being completely bony are totally inelastic. Pressure from within must of necessity push the orbital content forward and outward. Thus it becomes obvious that if the orbital muscles become unduly hypertrophied and the orbital fat becomes so edematous as to occupy most of



FIG. 113. Lateral view of a patient with severe exophthalmos and hyperthyroidism (Graham E. A. *Surgical Diagnosis*, Vol. II Philadelphia W. B. Saunders Co. 1930)

the orbital space the globus oculi must necessarily protrude. There is no other possibility.

Otolaryngologic Causes of Exophthalmos

Disease spreading to orbital walls and contents from adjoining tissues may cause proptosis. This of necessity must be differentiated from exophthalmos of thyroid origin. Inflammation is most often responsible in children and young adults; tumor in older people.

Since the adoption of modern antibacterial drugs paranasal sinus infection rarely produces orbital cellulitis. Ethmoid cells are the most frequent source in babies and small children since the eye socket is protected

only by the very thin lamina papyracea. In young adults particularly the beetle browed the orbit is generally infected through the frontal sinus. Otitis occurs then edema of the socket with pain and fever. The lids are dusky red, soft and swollen. If pus form in the orbit proper the globe is moved forward and outward or downward.

Acute ethmoiditis seldom produces orbital abscess or cellulitis requiring drainage. But if cellulitis results from acute frontal sinusitis trephination should be done through the inner floor without delay.

As a general rule tumors causing exophthalmos are benign when originating in the frontal sinus and malignant if arising in the maxillary or ethmoid. Most frontal growths are mucocoeles which grow slowly and rarely cause inflammation. Occasionally osteomas are seen. Both types should be removed completely by an external frontoethmoid procedure.

Sarcoma and carcinoma occur with about equal frequency the former at any age the latter chiefly at 40 year and older. Carcinoma of maxillary origin is more common than ethmoid and rarely frontal carcinoma is encountered. Nasopharyngeal tumors seldom reach as far as the orbit.

Anterior neoplasms cause pain in the upper teeth and cheek, buccal swelling, the thickening of skin and upward displacement of the eye. Ethmoid growths soon break into nasal and orbital cavities producing epiphora, diplopia, exophthalmos with palpable tumor, foul bloody discharge and severe pain. Wide surgical removal may be effective unless the deep cervical lymph glands are involved. If metastasis has occurred only palliative radiation is of use.

Tumors in Children During infancy and childhood the primary orbital tumors are hemangioma, optic nerve glioma, dermoid, teratoma and the enchymal tissue tumors.

Hemangiomas often extend far enough forward to cause visible discoloration. Growths in young people are usually radioactive.

Gliomas of the optic nerve though histologically benign may cause optic atrophy and blindness or invade the brain and distort the pituitary fossa. Tumors are excised intracranially unroofing the optic canal and orbit if necessary. The eye is then removed anteriorly.

Congenital tumors including dermoid and teratoma arise outside the muscle cone and may cause lateral or vertical displacement of the globe. Dermoids often grow at suture lines and penetrate the skull. Roentgenograms are made to show bony dehiscence. A neurosurgeon should collaborate with the ophthalmologist in the surgical treatment.

Undifferentiated sarcomas of the orbit are among the most malignant neoplasms of childhood the least dangerous being rhabdomyosarcoma. Immediate exenteration is ordinarily advisable preceded or followed by irradiation.

Tumors in Adults A common tumor of adults is hemangioma. The diag-

nodes may be confused by calcification and hyperostosis. Growths are usually nonmalignant in nature and radio sensitive.

Meningioma originating in or in the orbit quickly produces proptosis and optic atrophy, often hampers eye movement and generally causes hyperostosis. It is not found often in individuals under 30 years of age. True bone tumors are seen before the age of 20 in most instances.

So called mixed tumors of the lacrimal gland displace the eye downward and nasally and frequently decrease the flow of tears. They recur locally and destroy bone. Roentgen therapy is usually ineffectual.

Retrobulbar lymphomas are of all types ranging from benign to malignant and all are quite susceptible to radiation. The origin is ill defined and prognosis uncertain.

Tumors of Schwann's sheath such as neurofibroma, neurinoma, neurilemmoma and melanoma may begin initially in the orbit.

Although a great variety of lesions may emanate from neighboring tissues or metastasize from afar. In every unexplained case of exophthalmos diligent search is most essential.

Abnormal arteriovenous shunts from injury or other factor may cause pulsating protrusion of the eye with audible bruit and palpable thrill. Vertical extraocular muscles are usually paralyzed since lesions are often in the carotid sinus wall. In some instances craniotomy can be done and involved vessels ligated.

Either or both eyes may be thrust forward by systemic disorders including angioneurotic edema, infection and xanthomatosis such as Schulzer-Christian disease.

Progressive Postoperative Exophthalmos

This condition although not common has been and still is the most baffling problem confronting the physician and surgeon. It is frequently the only remnant of the disease that once existed. Its characteristic is to be progressive leading sometimes to almost complete extrusion of the eyeballs, total blindness and panophthalmitis with all its consequences.

Progressive exophthalmos is more common in men than in women. In this connection it is interesting to recall that Marine observed male rabbits to be more susceptible than female rabbits to the experimental production of exophthalmos.

The majority of thyrotoxic patients with exophthalmos recover fully after thyroidectomy. The thyrotoxic syndrome disappears altogether or almost completely. Exophthalmos however when present subsides more slowly. Sometimes it remains permanently stationary with no untoward effect on the patient.²²

In a few instances sometimes months or even years after thyroidectomy

exophthalmos reappears and follows a progressive course until the lids can no longer cover the bulbus. The lids become extremely puffy and the ocular movements more and more restricted. The conjunctiva becomes congested and swollen to such an extent that it herniates through the lids. Laceration becomes very annoying. Being unprotected the cornea becomes inflamed, finally ulcerates and pyrophthalmitis follows. In the meantime the eye sight has been totally lost. The only course open is enucleation; otherwise death will ensue. Ordinarily the patient has a low metabolic rate in the presence of these severe eye findings.

The theory that thyrotoxic exophthalmos and progressive postoperative exophthalmos are produced by the same mechanism seems justified. To be sure there are differences. In thyrotoxic exophthalmos the mobility of the eyeball is not impaired or at least very slightly impaired. In progressive postoperative exophthalmos the impairment is marked. The upward and downward rotation ceases first; later the inward and outward motions disappear. In thyrotoxic proptosis there is usually no chemosis. In the postoperative progressive exophthalmos, hyperthyroidism is usually the rule. In thyrotoxic exophthalmos the reverse is usually true, namely, hyperthyroidism is absent in the presence of the eye pathology.

In both forms of exophthalmos mydriasis is absent. In the two forms also the trophic orbital disturbances are the same. Changes in the retina occur in both forms of exophthalmos but only in the last stages of the disease.

In the last analysis, however, these two forms of exophthalmos must have a common origin. The trophic disturbances of the orbital muscles are probably primarily caused by stimulation of the sympathetic nerve, which in turn brings about trophic disturbances. Biological and chemical reactions must also play a part in the production of the syndrome.

One thing remains to be explained. Why is it that, even after all other thyrotoxic symptoms have subsided, exophthalmos still persists for a long time and sometimes permanently? Probably this happens because the eyeball, having protruded for so long a time, has lost the "right of domicile" in the orbit. It has acquired new relations; connective tissue and retrobulbar fat have filled the dead space left by the eyeball while it protruded, and it is difficult or even impossible for the globus oculi ever to return to its normal position.

Why is it that thyrotoxic thyroids do not all produce exophthalmos? We do not know. After seeing a large series of thyrotoxic goiters, one notices that in certain thyrotoxic patients the toxic effects of the hyperthyroid gland seem to center their deleterious effects upon certain organs or systems of organs. In some patients the cardiovascular system seems to be affected disproportionately to the other organs. In other patients it is the

gastrointestinal system that is heavily attacked by thyrotoxicosis with vomiting and diarrhea as cardinal complaints. In still other patients the ocular system is more markedly involved. This would lead one to believe that certain organs or systems of organs may be unduly sensitized to thyroxine while other are resistant to it. On the other hand the concept of sensitization as an activator may well have an opposite effect, namely to act as an inhibitor as for instance with the production of a low metabolic rate.

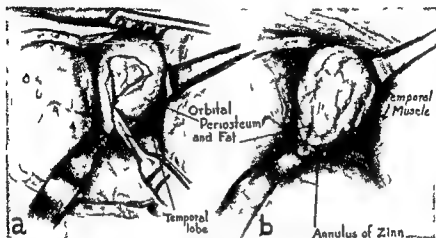


FIG. 114. Diagrammatic illustration of the various steps in the operation for intractable exophthalmos. A Through a parietal flap with the frontal lobe elevated the bones of the orbital roof have been removed with a rongeur. The orbital periosteum has been incised and the underlying fat is brought into the incised area. B There is an upward bulging of the retrobulbar fat and the retroocular muscles with a resulting diminution of the forward pressure on the eye. (Laher, F. H. *Surgery of the thyroid gland*. New England J. Med. 236: 46-69, 1947.)

Treatment of Exophthalmos

One must treat the thyrotoxicosis first. The earlier this condition is treated and cured the greater the chances that exophthalmos will subside and disappear. One should always remember that whenever ocular signs appear early in cases of thyrotoxic goiter the eye signs and the conditions that cause them if allowed to go unchecked will quickly become severe.

The Exophthalmometer. In the early stages of thyrotoxicosis exophthalmos is frequently diagnosed when in reality it is not present at least not yet. The presence of the Dührmle sign, namely retraction upward and downward of the eyelids is responsible for the mistaken diagnosis.

Measurements with the exophthalmometer will soon determine whether exophthalmos is present or not. Measurements in excess of 18 must be regarded as abnormal especially if there is a difference in the measurements of the two eyes.

Since patients with progressive exophthalmos are, in the majority of instances, hypothyroid, thyroid extract is given. To this iodine is added

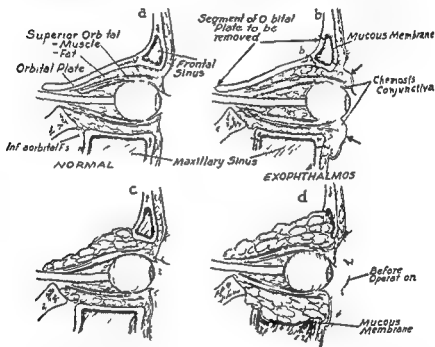


FIG. 115. Diagrams of the various steps in the operation for supraorbital decompression of the eyeball for intractable exophthalmia. The *a* are lateral views showing how the operation results in an increase in the space confining the eyeball. With such increase there is a regression of the exophthalmia (Lahey, F. H. *Surgery of the thyroid gland*, New England J. Med. 236: 46-62, 1917).

the idea being that it will be helpful if thyrotoxic signs are present and if not will act as a deterrent to the edema of the tissues.

Cervical Sympathectomy. Cervical sympathectomy, as it was performed, has been abandoned. The new antithyroid drugs have proved disappointing in alleviating exophthalmia except when hyperthyroid symptoms are present.

Electrocauterization of the hypophysis and its stalk. This procedure carries with it the danger of pituitary deficiency manifested by general weakness, a very low basal metabolic rate, sexual impotence, etc.

atrophy and hypoglycemia (McCulligh). However, some good results have been obtained.



FIG. 116 A Patient with severe exophthalmos. This photograph was taken several weeks prior to supraciliary decompression procedure. (All photographs in this series are through the courtesy of Howard C. Naffziger, Department of Neurological Surgery, University of California Medical Center.)

B Same patient, showing marked proptosis one week prior to surgery.

C Lateral photograph of the same patient taken the day before operation.

D Anterior view taken the day before operation, showing the rapid advancement of exophthalmos in one week. Note the ring of edema above lower eyelids.

Irradiation of the Pituitary This therapy has been found useful in a few cases, but has given totally negative results in others.

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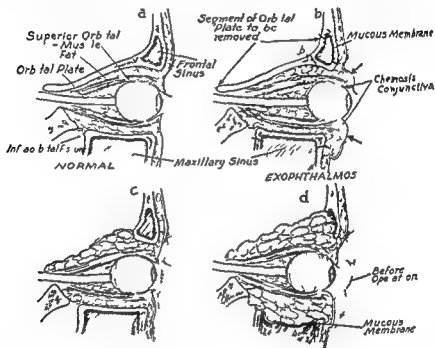


FIG. 115. Diagrams of the various steps in the operation for supraorbital decompression of the eyeball for intractable exophthalmos. These are lateral views showing how the operation results in an increase in the space confining the eyeball. With such increase there is a regression of the exophthalmos. (Lahey, F. H. *Surgery of the thyroid gland*. New England J. Med. 236: 46-62, 1947.)

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drug was given. Recurrence of the signs and symptoms were noted when the drug was stopped. Therefore treatment must be given for a long period of time.⁶¹

There appeared a study in the *Journal of Endocrinology* concerning the treatment of malignant edematous exophthalmos by surgical hypophysectomy. This procedure was performed after intensive treatment with all types of medical therapies. Following surgery there was a remarkable improvement in the exophthalmos. Histological examination of the tissue removed at surgery showed an increase in the numbers and in the secretory activity of cells that are considered to be the site of production of the thyroid stimulating hormone. It is of value to know that in some patients in whom hypophysectomy has been performed for malignant disease, clinical hypothyroidism developed within 4 to 8 weeks following operation. The thyroid gland itself has been found to have an increase in fibrosis and in other glands a slight increase in the height of the follicular epithelium cells was noted.⁶²

Orbital Decompression of Naffziger Orbital decompression consists of removing the superior orbital plate and unroofing and removing the bone covering the optic foramen. This will permit the orbital content to move upward and in consequence, will do away with the intraorbital forward push on the eyeball. It is mandatory to unroof the optic foramen so as to release pressure on the optic nerve. A pressure bandage over the tightly closed eyelids is necessary in order to push the eye backward. Orbital decompression should be done, especially when the optic nerves show signs of being destroyed or embarrassed.

Although this operation devised by Naffziger will not always abolish the unsightly exophthalmos, it will, if done in time, prevent ulceration in



E Photograph taken immediately following operation (Supraciliary decompression procedure performed by Howard C. Naffziger, University of California Hospital)

F Postoperative photograph of the same patient looking to the right

fection and, if loss of blood supply has not already taken place save the eye. It will obviously be of no value however to patients who are sent for operation when the eyeball is practically falling out of the orbital socket.

Recently several French investigators have used cortisone and corticotropin in the treatment of 15 patients with hyperthyroid edematous exophthalmos. In the cases studied the degree of exophthalmos was not directly proportionate to the severity of the hyperthyroidism. In fact some of the patients with the severest exophthalmia had hypothyroidism. The use of the steroids showed an improvement in the edematous exophthalmos in a matter of hours. The improvement manifested itself on the edema chemosis and the subjective symptoms particularly. Ocular protrusion was not reduced remarkably. The best results were obtained when the drug was administered early in the disease. The improvement continued as long as the

Hyperparathyroidism

NO DISCUSSION on disorders of the thyroid gland would be complete without some remarks on the parathyroid and its disorder. Most physicians and surgeons rarely consider hyperparathyroidism when they are studying a patient. For this reason the diagnosis may not be arrived at until the patient has harbored the disease for months or years.

Laboratory and Clinical Picture

Although there have been many excellent reviews on hyperparathyroidism the diagnosis unfortunately is not often accurately made. This may be due perhaps to the wide spread misbelief that diseases of the bone are a requisite in the clinical picture of hyperparathyroidism. It may also be due to the fact that some internists and surgeons believe that the diagnosis cannot be substantiated if only minimal hypercalcemia is present. It is well to remember that the presence of renal calculi is an indication that excessive parathyroid activity must be eliminated. In addition it is well to emphasize that hyperparathyroidism may at times produce only a minimal elevation of serum calcium. The power of the kidneys to excrete an increased amount of calcium may be severely taxed during the process of calcium excretion.

The excessive amount of calcium in the urine may be detected by the Sulkowitch test. This is a qualitative analysis of the urine. Although this test may also be found positive in other conditions it is nevertheless an available diagnostic aid in evaluating patients with hyperparathyroidism. The Sulkowitch reagent is a solution containing 2.5 Gm. of oxalic acid, 2.5 Gm. of ammonium oxalate, 5 cc. of glacial acetic acid and water to a final volume of 100 cc. When this solution is mixed with urine containing calcium a fine white precipitate of calcium oxalate appears within a few seconds. By mixing this reagent and urine one can differentiate between urine with no calcium (no precipitate), urine with a normal amount of calcium (moderate precipitate) and urine with an excessive amount of calcium (heavy precipitate).

The measurement of renal reabsorption of phosphorus appears to be a valuable diagnostic test for primary hyperparathyroidism even in patients

with moderate renal impairment Schaaf and Kyle⁹ reported that in healthy subjects, renal phosphorus reabsorption is about 91 per cent, whereas patients with primary hyperthyroidism have only about 58 per cent reabsorption. Their method utilizes blood and urine determinations of phosphorus in conjunction with endogenous creatinine clearance estimate of glomerular filtration rate. The ratio of reabsorbed to filtered phosphorus, multiplied by 100, is an estimate of the per cent of renal phosphorus reabsorption.

On occasion it may be necessary to employ the Bauer Sub diet as another valuable means of arriving at excessive parathyroid function. This diet contains approximately 135 to 150 mg of calcium per day. The diet is a neutral ash low calcium diet consisting of vegetable fruit meat cereals and oleomargarine. Butter, milk, cheese, cream and cereals fortified with calcium are prohibited. The patient is fed this diet for one week during this time the patient is not kept at bed rest. At the end of the week a 24 hour urine specimen is collected and the calcium content is quantitatively analyzed. The exact content of the diet is presented in Albright and Reifenstein's textbook.¹

A new test of parathyroid function involves the study of phosphaturia induced by calcium infusion. French authors reported the effects on phosphaturia of an infusion of 3.3 Gm. of calcium chloride in 500 cc. of isotonic glucose solution. A diuresis greater than 500 cc. in 3 hours was noted in control subjects, together with a decreasing hourly phosphaturia. This led to a 24 hour phosphaturia that was definitely lower than that before and during the first 24 hours after infusion, though the latter is often higher than the initial phosphaturia. In the patient with postoperative or idiopathic hypoparathyroidism who had not received treatment there was a decreased diuretic response and a frank hyperphosphaturic response both in the hourly and 24 hour specimens. There was no abnormal elevation of phosphaturia in the 24 hours after infusion. In patients with hypoparathyroidism who were treated these responses were attenuated or even reversed. In spasmodophilia (idiopathic normocalcemic tetany) and in the so-called endocrine cataracts there was no definite disturbance of the diuretic response and the 24 hours phosphaturia. On the other hand the hourly hypophosphaturia response was modified. It was established slowly and progressively in spasmodophilia and was retarded in the cataracts after a phase of complete absence during which there was transient hyperphosphaturia.⁴

The foregoing study on phosphaturia is another adjunct in the laboratory diagnosis of parathyroid disturbance. Although this is only a preliminary report nevertheless it may be employed in the borderline cases when every available diagnostic aid is needed in the evaluation of a patient's clinical picture. The value of this test is enhanced when one realizes that

it is fairly well established that the muscular symptoms presented by the patient are due to hypophosphatemia.

Primary hyperparathyroidism is usually the result of a solitary benign adenoma of one of the parathyroid glands. Rarely is this hyperfunction the result of all the parathyroid glands. Multiple adenomas and malignancy of the parathyroids is likewise not a common occurrence.

The clinical picture resulting from adenoma of the parathyroid is due to



FIG. 117. Gross specimen of a parathyroid adenoma (Attie, J. N., and Lickmutter, M. Diagnosis and treatment of hyperparathyroidism. New York State J. Med. 52: No. 19, 1951).

excessive secretion of the parathyroid hormone. The exact site of its action is controversial. However, for purposes of discussion it will be assumed that the primary function is to control the excretion of the phosphate ion by the renal tubule. In the presence of excessive hormone, phosphate excretion is increased, and the level of phosphate ion in the blood diminishes. As a result of the disturbance in the ratio between the calcium and phosphorus ion in the blood, both ions are withdrawn from the bone and a stimulus is provided for increased osteoblastic activity with its accompanying increase in the alkaline phosphatase of the blood. In this manner the characteristic biochemical features are produced, namely, high blood calcium, low blood phosphorus, and increased alkaline phosphatase. The elevation in the quantity

of calcium ion in the blood necessarily leads to an increased excretion of calcium in the urine

The symptom complex therefore falls into three categories

- 1 The result of high blood calcium
- 2 Excessive urinary calcium and phosphorus
- 3 Secondary bone changes

When symptoms result from an elevated blood calcium the diagnosis is

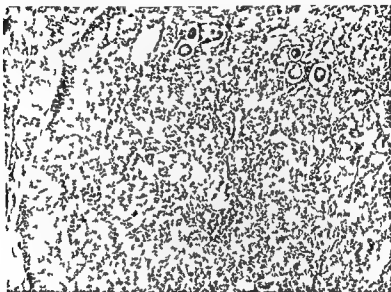


FIG 118 Photomicrograph (10 \times) of a parathyroid adenoma. The cytoarchitecture is that of parathyroid tissue composed of compact columns of opaque epithelium arranged in a palisade form. Much variation in the size and appearance of the columns is noted. Many areas are quite vascular where the cell columns are small.

difficult without laboratory studies because the symptoms simulate many functional disorders. These symptoms are

Muscle weakness

Fatigue

Anorexia

Nausea

Vomiting

Constipation

Lethargy

Bradycardia

Cardiac Irregularities

The hypercalcaemia and hyperphosphaturia in the early stages, may be

manifested merely by polyuria and polydipsia, which may be misinterpreted as diabetes insipidus. Later renal calculi develop and symptoms



FIG. 119 X-ray film of the right humerus demonstrating cystic bone disease in a 25 year old female with hyperparathyroidism

appear from renal colic, or superimposed renal infection, and still later renal insufficiency. The secondary effect on the bony structures leads to a variety of disorders. There may be one of the following.

Cysts



FIG 120 Roentgenogram of right femur showing a tumor fibrosa cystica (proven by biopsy) in a 50 year old housewife with hyperparathyroidism

Fractures

Tumors

Deformities

Absence of lamina dura

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Cysts

fact that in the former more parathyroid hormone is produced than is necessary whereas in the latter the increased production of the hormone is



FIG 12. Neoplasia in a patient with hyperparathyroidism (Atlee J N 11; Perlmutter M. Diagnosis and treatment of hyperparathyroidism. New York St J Med 52 1951)

at compensating calcium losses. Secondary hyperparathyroidism is therefore a physiological process that serves to protect the organism from a

Relationships Between Parathyroids and Bone Diseases

The mechanism of bone formation is not entirely understood but probably the parathyroid influences the process by maintaining an adequate concentration of calcium and phosphorus in the blood. A functional insufficiency of these glands leads to uncontrolled osteogenesis with calcification of the cartilages and ligaments in addition to increased density of the bones.

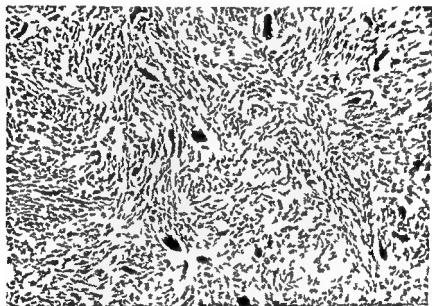


FIG. 121. Photomicrograph (150 \times) showing osteitis fibrosa cystica. This specimen was obtained via biopsy from the patient in figure 120. The characteristic feature of the lesion are minute smooth-walled cysts lined by cellular tissue and large giant cell tumor tissue.

already formed. A normal functioning of these glands insures the best bone formation. The calcium regulating action of these glands is demonstrated by the fact that if the blood calcium diminishes for causes other than a condition of the parathyroids, the body draws calcium from the bone to protect the organism against the dangerous consequences of hypocalcemia. When calcium decreases and tetany appears, the parathyroids become hyperactive (secondary hyperparathyroidism) and eventually become hyperplastic. It is therefore always necessary first to determine whether a case of hypocalcemia is the result of idiopathic hypoparathyroidism, in which case there would be no functional reaction of these glands. The difference between primary and secondary hyperparathyroidism lies in the

- 3 Lassitude
 - 4 Muscle weakness
 - 5 Cardiac arrhythmia and occasional low pulse
- B *Transportation and excretion of calcium*
- 1 Renal complications (lithiasis)
 - 2 Polyuria and polydipsia
 - 3 Enuresis nocturna and diuresis
- C *Skeletal system*
- 1 Pain in joints and bones
 - 2 Spontaneous fracture
 - 3 Cysts in long bones and skull
 - 4 Deformity of long bones
 - 5 Kyphosis, scoliosis or deformity of the thorax
 - 6 Waddling gait and inability to walk

Secondary Hyperparathyroidism

The pathologic characteristic of secondary hyperparathyroidism is hyperplasia of all the parathyroid tissue in contrast to the neoplastic involvement usually of one gland in the primary type. The hyperplasia is considered to be a compensatory response to metabolic disturbances resulting from renal or osseous disease. Infrequent cause is metastatic carcinoma of the bone, multiple myeloma, osteomalacia and rickets; however the most common cause is chronic renal disease. The essential feature appears to be a lesion congenital or acquired which leads to chronic renal failure of such an insidious nature that it is compatible with survival over a long period of time. While the presenting picture may be related primarily to the renal insufficiency, it is a peculiar characteristic especially in young individuals that the renal dysfunction may be so obvious that the individual is considered to be relatively healthy.

It is interesting to note that the Mayo Clinic reported 2 cases of intrathyroid hyperfunctioning parathyroid adenomata which were removed by incising the thyroid gland. A photograph of the microscopical sections appears in this chapter.

Familial Hyperparathyroidism

An interesting case report by Frohner and Wolgamot reviewed 5 cases of hyperparathyroidism in one family.

Case report. Evidence obtained from the study of all four of whom was found at operation to have one or more parathyroid adenomas supports the belief that primary hyperparathyroidism may be a familial disease (Rickets to osteomalacia) pregnant calcium deficiency and renal insufficiency all of which are known to produce diffuse hyperplasia of the parathyroid gland could not be considered as primary factors in the condition found in the 5 patients. Their consumption of milk was average.

hypocalcemia induced by causes other than parathyroid insufficiency. But it does at the same time impair the bones. If the hypocalcemia lasts long the bones undergo a marked loss of calcium because of the action of the parathyroid—especially in cases in which calcium absorption is deficient. Diseases in which secondary hyperparathyroidism may determine bone lesions are rickets, osteitis fibrosa cystica (Recklinghausen's disease), chronic renal insufficiency, and Fanconi's syndrome. In addition calcification of blood vessel or deposition of calcium in muscle tissue may be visualized by x-ray.

In 1954 Walton¹⁰ presented histories of two premature infants who presented signs of tetany such as twitching and tremors with and without convulsions. Antitetanic treatment consisted of the administration of calcium chloride and aluminum hydroxide gel in the formula and 10 per cent calcium gluconate intravenously. The occurrence of tetany in the two siblings led to the discovery of primary hyperparathyroidism in the mother. Surgical exploration of her neck was carried out and a parathyroid adenoma was removed from the inferior pole of the left lobe of the thyroid gland. These cases demonstrate the important role that prenatal factors may play in influencing the parathyroid state of newborn infant. The mechanism of intrauterine suppression of fetal parathyroid gland is incompletely understood. It is obvious that maternal primary hyperparathyroidism can exert transplacental influence and it seems likely that secondary hyperparathyroidism of pregnancy can also exert a transplacental influence. Since the former has an associated high serum calcium and the latter a low serum calcium the author suggests that the transplacental suppression is mediated not by calcium or phosphate ions but by parathyroid hormone. The author feels that the occurrence of tetany in premature or breast-fed infant or in a severe form in any infant should lead one to suspect hyperparathyroidism in the mother. Review of the literature reveals an apparently increased incidence of stillbirths, miscarriages and premature births in mothers with primary hyperparathyroidism.

The onset of hyperparathyroidism produces bizarre and ill defined symptoms which may easily be overlooked unless blood calcium studies are done. Norris concluded in his review that the average duration of symptoms before surgery has been from 5 to 7 years while Albright, Aub and Bauer¹¹ reported a case in which they believe the adenoma had existed for 39 years.¹²

Shelling and Keyser adequately classified the symptoms.¹³ They are presented here as a summary of the clinical picture of hyperparathyroidism.

A. Hypercalcemia

1. Hypotonia

2. Chronic constipation

- 3 Lassitude
- 4 Muscle weakness
 - 1 Cardiac arrhythmia and occasional low pulse
- B *Transportation and excretion of calcium*
 - 1 Renal complications (lithiasis)
 - 2 Polyuria and polydipsia
 - 3 Enuresis, nocturia and dysuria
- C *Skeletal system*
 - 1 Pain in joints and bones
 - 2 Spontaneous fracture
 - 3 Cysts in long bones and skull
 - 4 Deformity of long bones
 - 5 Kyphosis, scoliosis or deformity of the thorax
 - 6 Waddling gait and inability to walk

Secondary Hyperparathyroidism

The pathologic characteristic of secondary hyperparathyroidism is hyperplasia of all the parathyroid tissues in contrast to the neoplastic involvement usually of one gland in the primary type. This hyperplasia is considered to be a compensatory reaction to metabolic disturbances resulting from renal or osseous disease. Infrequent causes are metastatic carcinoma of the bone, multiple myeloma, osteomalacia and rickets; however the most common cause is chronic renal disease. The essential feature appears to be a lesion, congenital or acquired, which leads to chronic renal failure of such an insidious nature that it is compatible with survival over a long period of time. While the presenting picture may be related primarily to the renal insufficiency, it is a peculiar characteristic especially in young individual that the renal dysfunction may be so obscure that the individual is considered to be relatively healthy.

It is interesting to note that the Mayo Clinic reported 2 cases of intra-thyroid hyperfunctioning parathyroid adenomata which were removed by incising the thyroid gland. A photograph of the microscopic sections appears in this chapter.

Familial Hyperparathyroidism

An interesting case report by Frohner and Wolgamot reviewed 5 cases of hyperparathyroidism in one family.

Case report. Evidence obtained from the study of 5 siblings, each of whom was found at operation to have one or more parathyroid adenomata, supports the belief that primary hyperparathyroidism may be a familial disease. Rickets (osteomalacia), pregnancy calcium deficiency and renal insufficiency, all of which are known to produce diffuse hyperplasia of the parathyroid glands, could not be considered as primary factors in the condition found in these patients. Their consumption of milk was average.

and they had all received cod liver oil regularly in childhood. Only one had any impairment of renal function though all had renal disease (nephrocalcinosis in 3 and

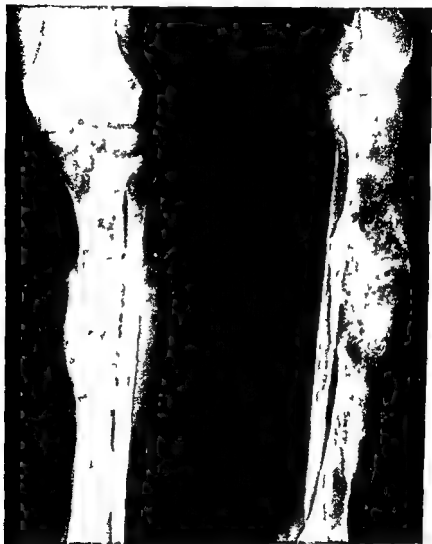


FIG. 123. Osteogenic sarcoma of the tibia arising in Paget's disease of the bone. This lesion is rarely associated with secondary hyperparathyroidism. It is of value to know that approximately 3 per cent of patients with Paget's bone disease develop sarcoma.

staghorn calculus in 1 and hematuria and renal colic due to stone in the last). The possibility of excess phosphate ingestion cannot be ruled out at present (the soil of the patients' home locality, however, does not differ significantly from Montana soil in general. Studies of the drinking water, which comes from a creek, are now under way.

he did not have diabetes. Hyperparathyroidism cannot be proved in this case, but during the last 15 years of his life he suffered from hypocalcemia, polyuria, nocturia and weakness—all classic symptoms of parathyroid disturbance. The patient's mother is in good health but he has a suspiciously low serum phosphorus level. A low serum phosphorus level was also found in an otherwise normal sibling of the patient's. Study of the rest of the family, consisting of another sibling and 7 children of the patient's, showed that all were normal. Investigation of the patient for a tumor of the pituitary gland and pancreatic islet cell tumors and a duodenal ulcer—two sets of ab-



FIG 121 Photomicrograph (150 X) showing intact bone disease. Fibrosis and irregular trabeculations composed of intercalated segments of bone with a mosaic like appearance are seen. This histologic picture is compatible with repeated destruction and formation of new bone. In this case the serum phosphatase was 139 units (calcium 128 mg and phosphorous 40 mg). For a differential diagnosis compare this picture with that demonstrating osteitis fibrosa cystica (figure 121).

normalities that have been described as occurring with hyperparathyroidism—proved negative.

Diagnosis

By means of the clinical picture and laboratory studies discussed at the beginning of this chapter one may make the diagnosis of excessive parathyroid activity. Succinctly it can be stated that diabetes insipidus may on occasion resemble hyperparathyroidism. For this reason this type of diabetes must be considered in the differential diagnosis.

During the past year Curtis and his associates³⁵ have observed 4 male patients in whom severe compression fractures of the vertebrae developed during the administration of cortisone or corticotropin, or both. Although demineralization of the skeleton is a recognized complication of cortisone therapy, the authors have emphasized the importance of possible pathological fractures when prolonged treatment of this type is employed. Under these circumstances especially if a patient develops a pathological fracture attention may be called to the parathyroid gland. Thus it is well to



FIG. 12a Pathologic fracture of the hip due to weakness of the bone. Bone lesions of this type may be associated with secondary hyperparathyroidism.

bear in mind that excessive cortisone therapy may result in bone lesions which may erroneously be attributed to hyperparathyroidism.

As to the laboratory studies as an aid in diagnosis the trinity which leads one to suspect hyperparathyroidism is high blood calcium, low blood phosphorus and an elevated alkaline phosphatase.

Diagnostic Sign in Hyperparathyroidism

At the Stanford University School of Medicine Fender¹⁴⁸ has described a sign which he has noted in hyperparathyroidism. He has described this as a 'watermelon sound' resulting from percussion of the patient's head.

In stead of the high pitched crack as evoked from a normal adult skull there emerged a booming low pitched note that reminded me of the sound



FIG. 126 X-ray of a humerus showing lymphosarcoma of the humerus (given by biopsy). This lesion is not usually associated with secondary hyperparathyroidism.

made by tapping on a watermelon. It turned out that the patient had hyperparathyroidism.

Tape recordings were made by placing a crystal type of Electrovoice microphone 1 cm. from the scalp. A Magnacorder type PT6AH was used

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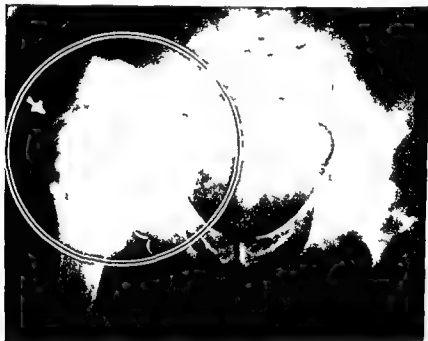


FIG 170 Pathologic fracture of the hip due to sarcoma of the bone. Bone lesions of this type may be associated with secondary hyperparathyroidism.

bear in mind that excessive cortisone therapy may result in bone lesion which may erroneously be attributed to hyperparathyroidism.

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The resulting skull was recorded in addition to an x ray photograph of the patient in question. The report of the radiologist indicates that the appearance of the skull is strongly suggestive of hyperparathyroidism.¹⁴⁸ This diagnostic sign is offered for the reader's own evaluation.



FIG. 129. Roentgenogram of the skull of a patient with hyperparathyroidism. Note the fuzzy appearance of the diploë bones (Fender T. A. Diagnostic sign in hyperparathyroidism. J. A. M. A. 154, March 17, 1951).

Treatment

The treatment of hyperparathyroidism is surgical. When a diagnosis of excessive parathyroid activity has been indicated as the etiological agent for the clinical symptoms presented in a patient, exploration of the neck is imperative. In all probability, an adenoma may be the cause for the symptom complex. Removal of the parathyroid tumor results in an amelioration of the symptoms.

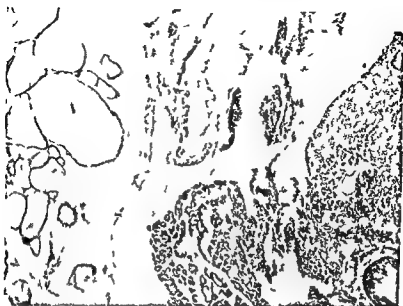


FIG 127 Microscopic section of a parathyroid adenoma found within the thyroid gland. The adenoma is seen lying in immediate apposition to thyroid tissue (hematoxylin and eosin stain $50\times$). It is noted that there is an absence of any intervening fibrous tissue septum which might represent a capsule. The tumor was found when the right lobe of the thyroid was divided in a longitudinal plane (Black B M. and Haynes A I. Intrathyroid parathyroid adenomas. Proc Staff Meet. Mayo Clin 24 No 16 1949)

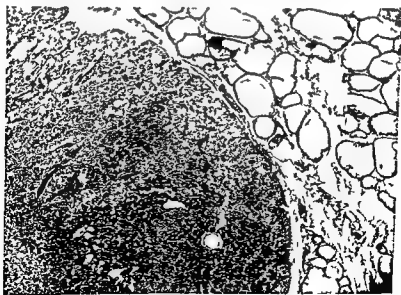


FIG 128 High power microscopic view of adenoma described in figure 127

| | C. & J. | B. & H. |
|-----------|---------|------------|
| Length | 6 mm | 3 to 15 mm |
| Width | 3 mm | to 4 mm |
| Thickness | 2 mm | 2 to 4 mm |

Fortunately when an adenoma is present it is much larger than a normal parathyroid. Thus its identity is more readily revealed. Even though a parathyroid adenoma is larger than a normal parathyroid gland it is often not difficult to locate this lesion. If the surgeon will recall that most parathyroid tumors are in locations near the thyroid vessels he will be rewarded on many occasions by finding the adenoma. If the surgeon follows the blood vessels especially the inferior thyroid artery he may find an adenoma migrating in the direction of the mediastinum or subclavicular area. The presence of an adenoma in the mediastinum is not unusual and should be related may be mentioned at the operating table.

Cutlow reported a case which well illustrates the situation.¹⁰ In a 50 year old man who case is reported the history and the blood calcium values indicated hyperparathyroidism. Surgical exploration of the neck disclosed no parathyroid adenoma. It was decided that at a second operation the superior mediastinum should be explored. This was done. However on the 4th postoperative day bilateral pneumothorax developed, it was followed by cardiac decompensation and death on the 5th postoperative day. Autopsy revealed a mass in the superior mediastinum which on microscopic study showed the typical picture of a parathyroid adenoma. This case emphasizes the necessity of exploring the mediastinum after fruitless neck exploration for parathyroid adenoma.

In view of the report from the Mayo Clinic it is apparent that a parathyroid adenoma may be found in the substance of the thyroid gland itself. With this knowledge as a basis it would seem logical to incise the thyroid gland itself when an accurate diagnosis of hyperparathyroidism has been made and surgical exploration in the usual manner has failed to reveal the pathology sought. Under these circumstances it would be well for the surgeon to incise the thyroid across the isthmus divide it completely in half and expose both lobes laterally. When this has been accomplished a parathyroid adenoma may be found in the inferior borders of either the right or left thyroid lobe.

Effects of Parathyroidectomy and Tetany on Liver Cell Permeability

Following the removal of a parathyroid adenoma certain effects may result which are not worthy of recollection. Underhill and Beatherwich¹¹ demonstrated that when two parathyroid glands are removed in dogs they

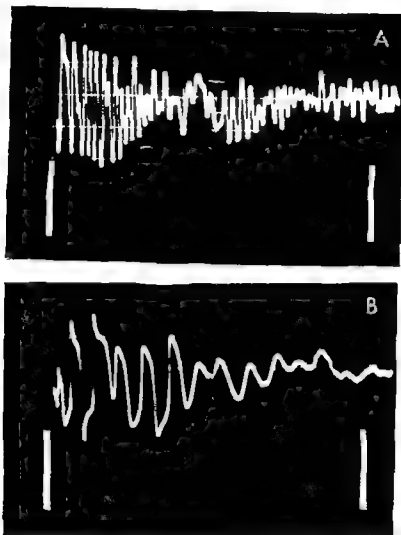


FIG 150-4 Oscillographic reproduction of the percussion notes of the skull of a normal adult *B* Frequency of the abnormal note in a patient with hyperparathyroidism in whom the so called watermelon sign was elicited. The frequency of a normal note is approximately 2600 per second. The frequency of the abnormal note is approximately 500 per second (Fender *F A* Diagnostic sign in hyperparathyroidism *J A M A* 154 March 17 1951)

From the point of view of surgical technique, it is well to remember that the parathyroid glands are very small. As a matter of fact they have been described as being about the size of an orange seed. Cowdry⁴⁷ and Biedl⁴⁸ measured the parathyroid gland in many anatomical specimens and their measurements were

of more than one mass should lead one to suspect the presence of carcinoma of the parathyroid gland. In addition, invasion of the recurrent laryngeal nerve is a strong indication that the lesion is malignant. The parathyroid cancer is usually three times larger than the usual hyperfunctioning benign adenoma. Adenoma is found in the region of the lower pole of the right or

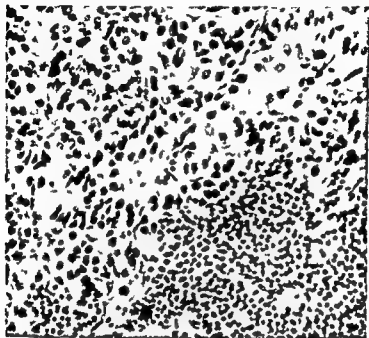


FIG 131 Photomicrograph ($\times 200$) of a parathyroid tumor removed from a 73-year-old housewife. This section shows both a benign and a malignant tumor. This is evidence for malignancy developing in a previously benign adenoma. Note the difference in size, shape and arrangement between the larger carcinomatous and the smaller adenomatous cells (Cope O. Surgery of Hyperparathyroidism Ann Surg 114: 706, 1911).

left thyroid lobe is a more common location for malignant lesions than those found in the upper poles.

When the specimen is examined in the laboratory, certain findings indicate carcinoma of the parathyroid gland. However, the usual pathological criteria cannot always be applied to the parathyroid glands. For example, cellular pleomorphism, giant nuclei, nests of tumor cells in blood vessels, or apparent invasion of the capsule are not sufficient evidence in the differential diagnosis of parathyroid tumors. The presence of mitotic figures, a trabecular pattern, tumor thrombi, and lymphatic invasion, however,

develop a marked drop in the blood sugar level. When these animals were sacrificed 4 days after parathyroidectomy it was found that the liver lost its entire glycogen content. There was also an elevation in the blood sugar during the 4 days after parathyroidectomy. When an injection of calcium lactate was given intravenously the blood sugar returned to a normal level and the symptoms of tetany which were in evidence were abolished. These investigators believe that in parathyroidectomized animal due to the calcium deficiency their livers lost glycogen resulting in a hypoglycemia. Therefore when this deficiency is corrected by means of the calcium lactate, the liver recovers its storage capacity and the blood sugar returns to a normal level.

Removal of the parathyroid glands, experimentally, causes hypocalcemia. This fall in blood serum calcium is followed by an increase in cell membrane permeability. The parathyroid hormone in the intact animal mobilizes calcium from the bones in order to maintain the normal level of calcium in the blood serum. With the removal of the parathyroid glands the loss of calcium from the circulation cannot be replaced and hypocalcemia results which leads to the loss of cell membrane semipermeability.

From a cardiac point of view certain changes may occur in the electrocardiogram following parathyroidectomy. The loss of calcium interfere with the conduction time of the heart and the R-T interval is altered. These changes are temporary and can easily be corrected by the administration of calcium.

Following parathyroid surgery it is possible that the patient does not have a satisfactory clinical improvement. If laboratory studies are performed and continued, high serum calcium persists in spite of the removal of one or two parathyroid adenomata. This laboratory finding indicates that remaining adenomatous tissue is present in the patient. Thought should then be given to a second operation with the possibility that another parathyroid adenoma is in an ectopic location.

Carcinoma of the Parathyroid Gland

The interpretation of parathyroid carcinoma as of now, is at the stage of indecision similar to the state of affairs in reference to thyroid cancer several decades ago. For this reason the diagnosis of parathyroid carcinoma can be intimated more accurately at the operating table than under the microscope.

At the time of surgery the diagnosis may be strongly suspected from the gross appearance of the adenomatous lesion. This is especially valuable when a frozen section may be more confusing than revealing. For example, local invasion of surrounding tissue, metastatic implants, or the presence

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must be considered as adequate signs on microscopic examination, that carcinoma of the gland is present.

Patients with parathyroid cancer are usually found in the early forty's. They are, therefore, younger than patients with adenomata. Although adenomata are more commonly found in women, the presence of parathyroid cancer is equally distributed in both men and women.

As previously stated, surgery is indicated for parathyroid carcinoma as well as benign adenomata. All tumor tissue must be removed at the time of operation. Removal of the thyroid lobe on the side involved with sacrifice of the recurrent laryngeal nerve may be necessary. The presence of metastatic involvement either to regional lymph nodes or contiguous structures demands that a radical neck dissection be performed. The utility of irradiation or radioactive iodine is problematical in parathyroid carcinoma. There is no objection to irradiation, especially when complete excision of the tumor cannot be performed.

Prognosis in parathyroid carcinoma is not very promising. Black¹⁰ states that 16 of 20 patients with parathyroid cancer reported in the literature are now dead. However, surgical intervention relieved the symptomatology for an average of 20 months even in those patients with known metastasis. The recurrence of the tumor is quite high and death is almost inevitable within 2 years if invasion of the tumor is macroscopically demonstrated at the time of surgery.

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Index

- Abortion spontaneous in hypothyroidism 81-88
- ACTH test in study of adrenal cortical and thyroid function 15
- Adenocarcinoma papillary 184 190-208 211
see also Cancer thyroidal
- Adenoma
benign as precursor of thyroidal cancer 188-189
as cause of primary hyperparathyroidism 236
fetal in endemic goiter 46
metastasizing 140
nontoxic 44-45
hemorrhage in 45
parathyroid 236 237 249 251
thyroidal illustration of 48
toxic 54 56
hemorrhage in 54
see also Hurthle cell adenoma
- Adenomatous colloid goiter see Goiter endemic
- Adrenal cortical hypertrophy
following thyroid administration 13
following thyroidectomy 15
- Adrenal thyroid relationship in theories of thyroid crisis 113
- Anatomy of thyroid 9-10
see also Thyroid gland
- Anoxia
in hepatic disease 113-120 123
after thyroidectomy prevented by tracheotomy 174
- Antithyroids
controversy concerning effects on thyroid gland 49
effects of on thyroid gland 110
- Antithyroid drugs 83
carcinogenic tenacity of 139
in management of thyroid cancer 204
physiologic action of 135-139 140
toxic effects of 139
see also Hyperthyroidism
- Atelectasis in myxedema 11-17
differential diagnosis between and congenitive heart failure 11-12
- Batherson's neurocirculatory
confused with hyperthyroidism 51
symptoms of 57
- Barbiturate effect on thyroid gland 49
- Bauer's diet a test for hyperparathyroid function 236
- Biochemistry of thyroid gland 16-18
see also Thyroid gland
- Bone disease and parathyroid gland 240-243
see also Parathyroid gland
- Calcium
elevated blood in hyperparathyroidism 237
a goitrogenic agent 45-46
metabolism of and parathyroid gland 48
- Cancer
of parathyroid gland 257-261
in thyroglottal anomalies 221-222
thyroidal 183-210
age distribution of 184
anatomic representation of 187
antithyroid therapy in treatment of 244
characteristics 109-110
classification of 163-165
determination of resectability 203-204
disseminated by surgeon 206-207
factors influencing treatment of 207-209
interstitial irradiation in treatment of 207
iodine radioactive in treatment of 207-208
indications and contraindications 203
metastases of and thyroid toxicity 38

Cancer—Continued

- palliative resection in treatment of 195-197
 - pathologic classification of 192
 - pelvic metastases from 198-199
 - primary 188-189
 - pulmonary metastases from 194-195-196-197
 - radiation treatment in 197-200
 - external 191-200-202
 - radical dissection in treatment of 195
 - recurrence after treatment 209-210
 - treatment 193-206
- Cardiac arrhythmia transient after thyroidectomy 110-172
- Carcinoma 188-194
- as indication for thyroid surgery in elderly patients 94
 - see also Cancer thyroidal
- Chlorpromazine in treatment of thyroid crisis 125-126
- Cholesterol levels and administration of thyroid extract 15
- Climacterium and thyroid disease 89-94
- see also Thyroid gland
- Colloid 9-14
- as vehicle of thyroid secretion 9
- Cretinism
- endemic 30-31-72-74
 - differentiated from sporadic cretinism 72-74
 - relation to endemic goiter 72
 - sporadic 30-72-74
 - see also Myxedema
- Crisis thyroidal 100-127
- early sign of 110
 - hyperthyroxemia 111-112
 - liver as pathogenic factor in 122-123
 - hepatic anoxia 123
 - hyperadrenalism 123
 - theories of 110-114
- Cyst
- branchiogenic anatomic location of 42
 - thyroglossal 217-219-220-221
 - surgical approach to 219
- Delphian node 185-186-188
- as sign of thyroid malignancy 185
 - as sign of thyroiditis 185

- De Quervain's thyroiditis 103-105
- Duct thyroglossal anomalies of 211-214
- Ectopic thyroid 211-212
- explanations of 211
 - sites of 212
- Empysema as complication of tracheotomy 181
- Endemic goiter see Goiter endemic
- Enzymes in thyroid gland 16-17
- Euthyroidism 29
- Exophthalmos 223-233
- as first symptom of pituitary adenoma 224
 - intractable operation for 229-230
 - otolaryngologic causes of 225-227
 - ethmoiditis 226
 - tumor 226-227
 - physical mechanism of 224-225
 - progressive postoperative 221-229
 - after thyroidectomy for thyrotoxicosis 224
 - as symptom
 - of hyperthyroidism 81
 - of thyrotoxicosis 21
 - treatment of
 - by cervical sympathectomy 230
 - by electrocauterization of hypophysis 230
 - irradiation of pituitary in 231-232
 - by orbital decompression 232
- Fibrolymphoid hyperplasia and thyroid toxicity 27
- Frenkel in differentiation of hyperthyroidism and neurosis 65
- Geomedicine
- definition of 35
 - in study of distribution of goiter 38
 - calcium as causative factor 45
 - in study of endemic goiter 38-39
- Goiter
- adenomatous
 - contraindications to radioiodine in 134
 - endemic and incidence of thyroidal cancer 168
 - recurrence after treatment 209

- benign metastasizing 18a
metastases from 156
see also Cancer thyroidal
- classification of 30-31
colloid 30-31
nodular 31
parenchymatous 30
simple 30-31
toxic 30-31
 primary 30
 secondary 30-31
see also Hyperthyroidism Thyrotoxicosis
- diffuse toxic anatomy of 24
endemic 38-48
 anatomy of 46-47
 fetal adenomas 46
 hyperplasia in resembling hyperthyroidism 46
calcium as gastrogenetic agent 42-48
illustration of 43
therapy prophylactic 39-42-43
 iodine administration in 39-42
 thyroidal response to iodine deficiency 39
world regions of 38-39
 map showing 44
- exophthalmic 41-22
thyroidectomy in 141
see also Hyperthyroidism primary
and incidence of cancer 188-189
intrathoracic 174-183 211 213 214
clinical characteristics 174
surgical techniques in 175-183
lingual 211 212 213 214
 surgical approach to 214 215
lymphoid *see* Struma lymphomatosa
nodular and carcinoma 188-193
nontoxic
 diffuse 29
 prepubertal 17
phantom 149-180
 Sibson's aponeurosis in 149 180
plaque 211 214 21 216
in premature infant 82 83
substernal 144-148
 clinical characteristics 144
 surgical techniques in 145-177
toxic 16 19 21 29
 enzymatic activity in 16
 thyrotrophic hormone in etiology of 12
see also Hyperthyroidism primary
Thyrototoxicosis
Craves' disease *see* Hyperthyroidism
Thyrototoxicosis
Cullen's disease *see* Myxedema
- Hashimoto's disease 21
see also Struma lymphomatosa Thyroid gland toxic
- Hepatothyroid relationship *see* Liver
Hormone thyroidal
 circulating 17
 synthesis of 16-17
 thyroxine as 11
 plasma hormone 11
see also Thyroxine
- Hurthle cell adenoma 18a
thyroidal 106-108
- Hygroma cystic of neck 73
- Hyperiodism 113
- Hyperparathyroidism 234-234
clinical picture of 234-239 242-243
cystic bone disease accompanying 238
diagnosis of 234-239
 hypercalcemia in 234
 renal phosphorus reabsorption in 234-239
 Sulkowitch test in 234
 watermelon sound in 246-249 250
familial 243-245
nephrocalcinosis in 241
primary caused by parathyroid adenoma 246
secondary 240-241 243
 differentiated from primary 240-241
symptoms of 237
treatment 249-251
 surgery in 249
- Hyperplasia diffuse in primary hyperthyroidism 64
- Hyperpyrexia as symptom of thyroid crisis 109-110
- Hyperthyroid crisis *see* Crisis thyroidal
- Hyperthyroidism
 abnormal influence of on somatic physiology 61
 and abortion spontaneous 87-88
 apathetic 93
 illustration of 55

Hyperthyroidism—Continued

- mistaken for heart disease 56
- borderline and psychosomatic symptoms 57-59
- in children
 - diagnosis and differential diagnosis 78-81
 - response to iodine in 79
 - etiology 76
 - symptoms 76-78
- clinical picture of 19-50
- diagnosis of 27
- differentiated from functional disturbance 58-59
- effect of iodine on 14
- etiology of 22-27
 - emotional shock in 22-23
 - iodine insufficiency in 23-24
 - nervous mechanism in 22
 - thyroid hormone excessive elimination in 22
- exophthalmos as complication of 223
- incidence of 22
- indications for surgical treatment of
 - in elderly patients 93-94
- management of 130-166
 - antithyroid drugs in 135-140
 - see also Antithyroid drug
 - surgery 140-164
 - see also Thyroidectomy
- and menopause 92-93
- symptoms common to 93
- mental attitude of patients with 51-65
 - distinction between psychosomatic and borderline hyperthyroid symptoms 57-59-61
- mental symptoms in 57-65
- muscular dysfunction complicating 176
- myxedema gravis in 126-129
- and neurosis 61-65
 - Frenkel in differential diagnosis 65
- phobia as symptom of 59-61
 - classification of types 59
- and pregnancy
 - abortion following no treatment 86
 - liver streptococci associated with 84
 - management of 85-86
 - radioactive iodine contraindicated 86

prepubertal 71-78

primary

- clinical characteristics of 20
- confused with climacterium 59-
- contrasted with toxic adenoma 55
- developmental stage of 2a
- as endocrinopathy 19
 - organs affected by excessive thyroid function 19-20
- and exophthalmos illustration of 85
- illustration of 85
- microscopic view of diffuse hyperplasia in 64
- recurrence after treatment 209
- unknown etiology of 19
- radioactive iodine in treatment of 50
- iodine
 - reserpine in management of 50
- résumé of treatment 208-209
- role of liver in see Liver
- signs and symptoms of 21
- toxic symptoms of similar to neurotic manifestation 62-63
- treatment 81-83
 - antithyroid drugs 81-82
 - psychotherapy 82
 - thyroidectomy 81-82

Hyperthyroemia

- cause of thyroid crisis 111-112
- see also Crisis, thyroidal

Hypocalcemia following parathyroidectomy 252

Hypothyroidism 30-31

- cerebral dysfunction in 70
- thyroid extract in therapy of 70
- and cretinism 72-74
- distribution of hair in children with 73
- functional response of adrenal cortex in 15
- thyroid extract in etiologic study of 71

Infection pulmonary as complication of tracheotomy 181

Iodine

- content of anomalous tissue as test of thyroidal character 214
- in counteracting autogenic action of calcium 15

- deficiency of
 in endemic cretinism 2
 and endemic goiter 38
 insufficient supplies of in etiology of
 hyperthyroidism 23-24
 radioactive
 contraindications to use of 131
 carcinoma formation 134
 destruction of thyroid tissue by 204
 effects of 131 134
 isotopes of 131
 physiologic action in suppressing hy-
 perthyroidism 130-131
 in treatment of thyroid cancer
 207-208
 see also Cancer, thyroidal
 resistance to action of thyroid crisis
 112
 response to in differential diagnosis of
 hyperthyroidism 49
 Iodothyroglobulin
 metabolic function of 12
 and thyroxine 11
 see also Thyroxine
 Liver
 disease of and anoxia 119-122
 pathological findings in 122
 and hyperthyroidism 118-119
 laboratory tests on in thyroid disease
 116-117
 preoperative preparation affecting in
 thyroid surgery 124-125
 relationship with thyroid gland 114-
 117
 clinicopathologic evidence for 114-
 119
 Liver cell permeability of after para-
 thyroidectomy followed by tetra-
 ny 251-252
 Lymphadenopathy, cervical, anatomy
 of 47
 Lymphosarcoma 106
 of humerus 247
 Maternal theory as explanation of thy-
 roid disturbances 76
 Menopause
 and hyperthyroidism *see* Hyperthy-
 roidism
 symptoms of confused with primary
 hyperthyroidism 83 93
 Menstruation
 effect of thyroidal therapy on 56-57
 in euthyroid patients 56
 Mental symptoms
 common to hyperthyroidism and men-
 opause 90
 mistaken for hyperthyroidism 57
 failure of thyroidectomy in 51
 Metabolic rate
 ambiguity of 91
 compared with other tests of thyroid
 function 28-29 8
 in diagnosis of hyperthyroidism 27
 3 5 3 triiodothyronine and in myx-
 edema 16
 and thyroxine 11-12 7b
 see also Thyroid gland
 Mikulicz's disease 103
 Myasthenia gravis and hyperthyroid-
 ism *see* Hyperthyroidism
 Mydriasis 274 27b
 Myxedema
 a cites in 71-72
 calcium retention in 48
 cardiac enlargement in 69
 changes in hands in 68
 clinical characteristics of 20
 44 complication after thyroidectomy
 169
 differentiated from congestive heart
 failure 71-72
 electrocardiographic abnormalities in
 63
 facial appearance in 61
 following radioactive iodine 137
 following removal of ectopic thyroid
 tissue 211
 iodine deficiency in 74
 juvenile with goiter illustration of 73
 in management of thyroid cancer 204
 mental symptoms in 90-91
 psychoses 9
 microscopic view of pathologic tissue
 in 67
 primary Thyrotoxic in differential di-
 agnosis of 206
 prolaid in treatment of 68
 skin tests for in children 14

- Myxedema—Continued**
 in struma lymphomatosa after thyroidectomy 102
 symptoms of 30-31 67
 thiocyanate following thyroidectomy 66-74
 3 5 3 triiodothyronine in treatment of 16
 after thyroidectomy 81
- Neck**
 anatomy and physiology of in relation to thyroidectomy 141-144
 tumors of
 classification 38
 as to location 36
- Neck masses**
 differential diagnosis of 33-34
 etiologies of 33
 recognition of 32-38
 procedures in 32-36
- Nerves** cervical anatomy and physiology of in relation to thyroidectomy 147-149
- Nervousness** as symptom in toxic hyperthyroidism 62
- Neurosis**
 and hyperthyroidism 61-65
 present concept of 61
- Nontoxic nodular goiter** *see* Goiter endemic
- Otitis fibrosa cystica** 239 240 242
- Paget's bone disease** 244 245
- Paraaminosalicylic acid** antithyroid action of 140
- Parathyroid gland**
 adenoma of 251
 and calcium metabolism 48
 cancer of *see* Cancer of parathyroid gland
 dimensions 251
 effect of radioactive iodine on 134
 relationship to bone diseases 240-243
 résumé of history of 1-3
 tests of function 235
 Bauer Aub diet in 235
 phosphaturia 235-236
 in thyroidectomy 157
 transplantation of after accidental removal 157-158
 see also Hyperparathyroidism
 Parathyroidectomy effect of on liver cell permeability 251-252
 Physiology of thyroid 11-15
 see also Thyroid gland physiology of
 Phobia
 in menopausal patients with thyroid disease 90
 as symptom in hyperthyroidism 59-61
 Pituitary gland
 relationship to thyroid gland 223-224
 and secretion of thyrotrophic hormone 12
 and synthesis of thyroid hormone 18
 in thyroid disease at menopause 91
 Pituitary gonadal endometrial axis relation of thyroid to 86
 Pituitary thyroid axis 13-14
 Potassium perchlorate in treatment of thyrotoxicosis 137-138
 Potassium thiocyanate in treatment of hypertension toxic thyroidal manifestation of 66 69
 Pregnancy in patients with hyperthyroidism 83-86
 Primary hyperthyroidism *see* Hyperthyroidism primary
 Proptosis congenital confused with exophthalmos 80-81
 Psychoneurotic states simulating hyperthyroidism 57-58
 Psycho- caused by neuroendocrine imbalance 70
 Plummer's disease *see* Adenoma toxic
 Puberty and physiological enlargement of thyroid 7a
 Pulse rate in diagnosis of hyperthyroidism 27
- Radioactive iodine** *see* Iodine
 Radioiodine
 combined with triiodothyronine in test of thyroid function 29
 uptake of in diagnosis of thyroidal disease 28 29
 procedure 28
 Radium in treatment of thyroid cancer 202

- Reproductive function and thyroid gland 87-88
see also Thyroid gland
- Riedel's struma 95-101
 confused with struma lymphomatosa 95
 differentiation from struma lymphomatosa 97
 histologic 100
- Sarcoidosis 105
- Sarcoma
 bone 246
 osteogenic 244
- Sibson's aponeurosis *see* Goster phantom
- Sjogren's disease 105
- Stenosis tracheal as complication of tracheotomy 182
- Sterility effect of thyroidal therapy on 88-89
- Struma lymphomatosa 95-103
 clinical picture of 97-98
 diagnosis 98-99
 differentiation from Riedel's struma 97
 histologic 100
 etiology and pathology 95-97
 histologic section of 96
 lesions confused with 98
 prognosis in 102
 treatment 99-102
 surgery 99
- Struma ovarii 215-216-217-218
see also Teratomata
- Tachycardia thyroxine in causation of 12
- Teratomata 211-215-216
- Tetany
 effect on liver cell permeability 251-252
 following thyroidectomy 164-166
 in hyperparathyroidism 242
- Tetraiodothyronine *see* Thyroxine
- Thiocyanate in treatment of hyperthyroidism 130
- Thiouracil 137-138-139
 aid outcome of pregnancy 83
 3,5,3-triiodothyronine 16-18
 in treatment of myxedema 16
- Thymus gland
 as etiological factor in thyroid crisis 112
 histologic appearance of in myasthenia gravis 128
- Thyrocardiac disease 93
- Thyroglobulin 14
 hydrolysis of in thyroid gland 16-17
 proteolysis of forming free iodinated amino acid 16-17
 proteolytic transformation into thyroxine and triiodothyronine 17
- Thyroglossal anomalies 211-217
 carcinoma in 222-223
- Thyroid
 accessory distinguished from ectopic gland 212-213
- Thyroid gland
 anatomy of 9-10
 colloid 9
 illustration of 10
 isthmus 9
 lobes 9
 lobular relationships view of 201
 pyramidal lobe 9
 weight 9
 tissue substances in types of 9
 anomalies of *see specific subject headings*
 anoxia in diseases of liver damage following 119-122-123
 antibiotics effect of on 49
 antitumor interrelationship 12
- biochemistry 16-18
 amino acids in 16-17
 enzymes in 16
 functions of 18
 hydrolysis of thyroglobulin 16-17
 pituitary and synthesis of thyroid hormone 18
 synthesis of thyroxine 16
see also Thyroxine
 3,5,3-triiodothyronine 16
- classification of primary malignant tumors of 192
see also Cancer thyroidal
- cancer of *see* Cancer thyroidal
- characteristics of on physical examination 34-38
- colloidopathy in 25-26
- crisis of *see* Crisis thyroidal

Thyroid gland—*Continued*

- diagnosis of diseases confused with metastatic tumors 40-41
- disease of and chloasma 89-94
- role of pituitary gland in 91
- ectopic *see* Ectopic thyroid
- enlargement of 19
 - caused by hemorrhage 51-53
- and epithelial cells as center of function 26-27
- extract of
 - age dose schedule in myxedema 71
 - effect on adult myxedema 71
 - in therapy of hypothyroid cerebral dysfunction 70-71
- functions of
 - in calcium metabolism 48
 - drugs in study of 13
 - methods for determining
 - basal metabolic rate 27
 - blood protein bound iodine level 28-29
 - McWhirter Freiburn metabolic calculator 27
 - pulse rate 27
 - radioactive iodine uptake 23
 - serum cholesterol level 28
- hemorrhage in 51-56
 - chronic 55-56
- hypertrophy of and inadequate thyroid secretion 12
- method of examining illustration of 39
- normal
 - hypertrophy of in pregnancy 84
 - microscopic view of 62
- pain in 51-56
- physiological enlargement of 7a
- physiology of 11-15
 - thyroxine in 11
 - see also* Thyroxine
- relationship to liver *see* Liver
- and reproductive function 87-88
- résumé of history 1-8
- spheres of influence 20
- toxic six progressive phases of 26-27
- toxicity
 - criteria in 27-32
 - see also* Hyperthyroidism Thyrotoxicosis

Thyroidectomy

- and adrenal cortical hypertrophy 1a
 - advantages of in hyperthyroidism 141
 - complications following 167-182
 - air embolism 168
 - hemorrhage 167-168
 - thyroid crisis 167-169
 - see also* Crisis thyroidal
 - tracheal injury 168
 - failure in mental symptom mistaken for hyperthyroidism 5c
 - in management of hyperthyroidism in pregnancy 85
 - postoperative care in 169-170
 - practical aspects of (operative technique) 141-164
 - results of proving relationship between thyrotoxicosis and exophthalmos 223
 - in struma lymphomatosa 99-100
 - tetany following 164-166
 - hypercalcemia 166
 - treatment 16a
 - thiocyanate myxedema following 66-74
 - see also* Myxedema
 - tracheotomy elective after *see* Tracheotomy
 - transient cardiac arrhythmia after 1d
 - electrocardiograms in 171-172
 - treatment 171
 - in treatment
 - of hyperthyroidism 81-82
 - of thyroid cancer 20a-206
 - see also* Cancer thyroidal
- Thyroiditis 9a-10b
- chronic colloidophagy in 2a
 - indicated by thyroidal pain 53
 - nonsuppurative treatment of 10b
 - recurrence after treatment 209
 - see also* De Quervain thyroiditis Riedel's struma Struma lymphomatosa
- Thyrotoxic myopathy 126-127
- Thyrotoxicosis 124
- calcium excretion in 48
 - as cause of liver damage 115
 - exophthalmos in 223-225
 - caused by pituitary disturbance 273
 - fulminating *see* Crisis thyroidal
 - and iodine administration 14

- iodine metabolism in 21-22
 juvenile 82
 potassium perchlorate in treatment of 137-138
 primary 30
 symptoms in 21
 secondary 9-31
 symptoms in 21
 selectively affecting organ systems 228-229
 and spontaneous abortion 86
see also Hyperthyroidism
- Thyrotrophic hormone
 alteration of epithelial cells by 26-27
 as cause of thyrotoxicosis and exophthalmos 23
 and colloidophagy 25-26
 in etiology of toxic goiter 12
 in exophthalmic goiter 12
 in goiter without exophthalmos 12
 inactivation in thyroid gland 13
 and thyroidal hypertrophy 12
- Thyroxine
 acceleration of food oxidation by 12
 as active thyroid hormone 11
 as autocoid of thyroid 11
 effect on renal calcium threshold 48
 function of 11
 relation to triiodothyronine 17-18
 synthesis of 16-17
 in test for hyperthyroidism 29
- Thyropar following thyroidectomy for cancer 203-206
- Toxic goiter *see* Goiter toxic
- Toxicity of thyroid gland *see* Hyperthyroidism
 Thyroid gland
- Trachea compression of by goiter 144-145
- Tracheotomy
 complications of 181-182
 elective after thyroidectomy 142-144
 emergency 173
 necessitated by nerve injury in thyroidectomy 151
 technique of at thyroidectomy 180
 removal of tube 181-182
 in thyroidal cancer for relief of obstruction 197
- Triiodothyronine 16-18
 relation to thyroxine 17-18
 see also Thyroxine
 synthesis of 17
 in test for hyperthyroidism 29
 see also 3,5,3 triiodothyronine
- TSH *see* Thyropar
- Vision loss of in thyroid disease *see* Exophthalmos